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BULLETIN OF
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THE PHYSIOLOGICAL FACTORS WHICH GOVERN INERT GAS EXCHANGE

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The decay constants (k_j) of the equation of inert gas exchanges are the roots of an algebraic equation of degree $n + 1$, where n is the number of distinct absorbing tissues. The coefficients of this equation can be obtained numerically by certain independent experiments to measure the tissue parameters. Graphical solution of this equation yields theoretical values of the k_j. Combining these constants with the numerical values for the partial derivatives of the k_j then gives the per cent rate of change of the k_j as any one tissue parameter varies by a given fraction of its normal range. A numerical example of these calculations shows good conformity with experiment, and permits a quantitative estimate of variations in the speed of gas exchange from a knowledge of changes in the physiological state.

A central problem in aereo- and submarine physiology is the control of the rate of inert gas exchange in such a way that personnel do not develop the "bends" or "chokes". For either selection or therapeutic purposes it is therefore indispensable to know the factors which govern the exchange and the effectiveness of each. The following is an attempted solution of the problem based on an elementary mathematical analysis which we have presented elsewhere (Smith and Morales, 1944a, 1944b; Morales and Smith, 1944).

Tissue regions (Figure 1), of which the entire body is a distinct parallel arrangement,[1] absorb[2] inert gases in a manner described by the equation:

* The opinions expressed in this article are the private ones of the writers, and are not to be construed as reflecting the policies of the Navy Department or the Naval Service at large.

[1] We have shown elsewhere (Morales and Smith, 1945) that tissues may be arranged in three essentially distinct ways, of which this is one. The other two arrangements predict the loss of two exponentials at a time when the number of distinct absorbing tissues is reduced by one. Under similar circumstances, with a competitive parallel arrangement, only one exponential should be lost. As A. Behnke pointed out in personal communication, the use of helium is practically tantamount to reducing the number of distinct tissues by one, and helium exchange can be described by *one* less exponential than the exchange of nitrogen or krypton. This fact, plus the evidence alluded to later, forms the basis for our choice of arrangement.

[2] Or, with suitable changes in the boundary conditions, desorbs.

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$$\phi(t) = \phi(\infty) - Q_0 e^{-k_0 t} - Q_1 e^{-k_1 t} - \cdots - Q_n e^{-k_n t} \qquad (1)$$

where $\phi(t)$ is the amount of gas taken up to time t, and $\phi(\infty)$ is the asymptotic (steady state) amount; n is the number of tissues, and the Q's and the k's are constants depending on the physiological state of the limb and the properties of the gas.

SCHEMA OF A TISSUE REGION
COMPETITIVE PARALLEL

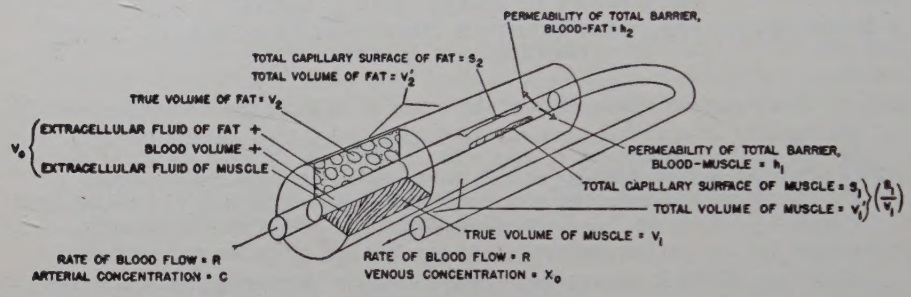

FIGURE 1

We consider that the parameters of the phenomenon are the following quantities:

R[cm^3 sec^{-1}] = rate of blood flow through the limb,

V_0[cm^3] = total amount of fluid outside of cells, including the blood volume,

and for the ith tissue:

α_i = concentration in blood/concentration within cells, at equilibrium.

h_i[cm sec^{-1}] = cell membrane permeability,

V_i[cm^3] = total cellular volume,

$\frac{S_i}{V_i}$ [cm^{-1}] = capillary surface/gross volume of tissue.

It is furthermore convenient to define the function,

$$\pi_i = \alpha_i h_i \frac{S_i}{V_i}.$$

Now it has been shown by several authors (Underwood and Diaz, 1941; Jones, 1941; Smith and Morales, 1944b) that equation (1) taken as a purely empirical fit, describes gas exchange data with remark-

able precision. This is true in particular of measurements of radioactive inert gas exchange by various tissue regions (Lawrence-Jones technique), to which we will turn presently. In such a procedure the decay constants, k_j, can be most conveniently determined by graphical analysis on arith-log paper. The order of magnitude of such constants is therefore well established. On the other hand, the parameters listed above can all be measured or estimated independently of gas absorption experiments (*vide infra*). When the values of these parameters are incorporated into the equations, the *theoretical* values of the k_j may be computed. It is proposed here to demonstrate the theoretical determination of decay constants, to show a favorable comparison with empirically obtained values, and finally to consider the effect of varying the physiological state on the decay constants, hence on the speed of inert gas exchange.

Values of the k_j are determined by [Smith and Morales, 1944a, equation (9)]:

$$V_0 k_j + \sum_{i=1}^{i=n} \frac{h_i S_i k_j}{\pi_i - k_j} - R = 0, \tag{2}$$

the left member of which is a polynomial of degree $n + 1$. In mammalian systems the number (n) of absorbing tissues is practically two, i.e., a tissue region is composed of aqueous tissue, fat, and bone, the last being essentially non-absorbing.

Clearing equation (2) of fractions for the special case, $n = 2$, we obtain

$$\begin{aligned} k_j^3 - & \frac{(\pi_1 + \pi_2) V_0 + \pi_1 \frac{V_1}{\alpha_1} + \pi_2 \frac{V_2}{\alpha_2} + R}{V_0} k_j^2 \\ & + \frac{\pi_1 \pi_2 \left(V_0 + \frac{V_1}{\alpha_1} + \frac{V_2}{\alpha_2} \right) + R(\pi_1 + \pi_2)}{V_0} k_j - \frac{R \pi_1 \pi_2}{V_0} = 0, \end{aligned} \tag{3}$$

where the subscripts 1 and 2 denote aqueous tissue and fat respectively. On substitution of values for the tissue parameters equation (3) becomes a numerical cubic, which on graphical solution gives three decay constants, k_0, k_1, k_2.

We may now differentiate equation (3) partially and obtain,

$$\begin{aligned}
\frac{1}{k_j}\frac{\partial k_j}{\partial R} &= \frac{\omega_j}{k_j}, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial (h_s S_s)} &= \frac{\omega_j k_j}{(\pi_s - k_j)^2}, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial \alpha_s} &= \omega_j V_s \left(\frac{\pi_s/\alpha_s}{\pi_s - k_j}\right)^2, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial V_0} &= -\omega_j, \\
\frac{1}{k_j}\frac{\partial k_j}{\partial V_s} &= -\frac{\omega_j}{\alpha_s}\left(\frac{\pi_s}{\pi_s - k_j}\right)^2,
\end{aligned} \tag{4}$$

with

$$\omega_j \equiv \frac{1}{V_0 + \sum_{i=1}^{i=n} \frac{V_i}{\alpha_i}\left(\frac{\pi_i}{\pi_i - k_j}\right)^2} > 0$$

corresponding to the per cent changes in the k_j for cgs unit change in a tissue parameter. These derivatives need only be corrected in a physiological sense in order to answer fully the problem we proposed to solve. By this we mean, for example, that a change of 1 cm^3 in volume of muscle is manifestly not the physiological equivalent of a change of 1 cm^3 sec^{-1} in rate of blood flow. We may, however, make these changes comparable by finding the per cent change in the k_j's when tissue paramters vary by, say, 10% of their normal range. Multiplying the differential coefficients by such factors then gives the final desired result.

The methods for obtaining values of the tissue parameters are various, and will be considered in order.

The average rate of blood flow over a three hour period can of course be measured by a water or air plethysmograph.[3]

The total amount of fluid which is outside of the cells is the sum of three contributions: (1) The true *blood volume*, which can be approximated as being equal to the volume change of a limb in passing from a very cold to a warm environment. (2) The *free-space of muscle.* Since Cl^{-1} does not penetrate muscle cells, any "chloride space" method (Fenn, 1936) gives the free space fraction for muscle. This value (18%) can also be checked theoretically, assuming quasi-close packing of cylindrical muscle fibers. The free space fraction

[3] The cgs dimensions for flow are cms^3 sec^{-1}, but in mammalian physiology it is customary to express blood flow in cubic centimeters of blood per 100 cubic centimeters of tissue.

times the total volume then gives the free space. (3) The *free space of fat.* Since the chloride method has not been shown to be applicable to fat tissue for the reason that, unlike the situation in muscle, the Cl^{-1} may be absorbed by the cells, recourse was sought in the value for the theoretical free space fraction of close packed ellipsoids, which can be shown to be 26%.[4] Again, this fraction times the total volume yields total free space.

The partition coefficients can be measured directly (Loomis, 1941).

The ratio of capillary surface/volume of tissue was judged from the work of I. Gersh and M. A. Still (1945), with due allowance for the differences which can be expected to exist in the human hand.

The plasma membrane permeabilities probably involve the greatest error of all of these determinations, since for virtually all systems they are known little more than by the order of magnitude. The computations of H. D. Landahl (1939) show oxygen permeability to be of the order of 10^{-5} cm sec^{-1}. Furthermore, the data of F. M. Müller (1941) and of others (see *International Critical Tables*) show that the permeabilities of oxygen and krypton are probably very similar. Guided by Professor S. C. Brooks' opinion that fat cells may have a higher h for krypton than do muscle cells, we have tentatively assumed 2×10^{-5} and 1×10^{-5} respectively as the krypton plasma membrane permeabilities of fat tissue and muscle.

It will be noted that when dealing with surface, we have spoken about *capillary* surface, while in dealing with permeability we have used *plasma membrane* values. This we feel is justified because the physiological behavior of the gross barrier will be governed by the limiting factors which go to make it up.[5] If such is the case, then certainly the limiting surface is that of the capillaries, and the limiting permeability that of the plasma membrane.

The total volumes were estimated from roentgenographs of hands.

Use of the foregoing techniques can be illustrated by a case of absorption of radioactive krypton by the hand. When measurements

[4] This is based on a simple generalization of the calculation which leads to the same values for close-packed spheres. In histological section, fat cells appear compressed, hence not subject to being treated as rigid ellipsoids; however, a number of observations by Ens. Mary Still and one of us (MFM) were enough to show that surviving fat cells in isotonic solution are truly arranged in the hexagonal lattice of rigid ellipsoids.

[5] This can be easily shown analytically by solving the transfer problem for a double barrier. If the permeability of the first membrane and the surface of the second are assumed to be much greater than the corresponding quantities for the other membrane, then the problem degenerates to one of transfer across a membrane having the lower permeability and the smaller surface.

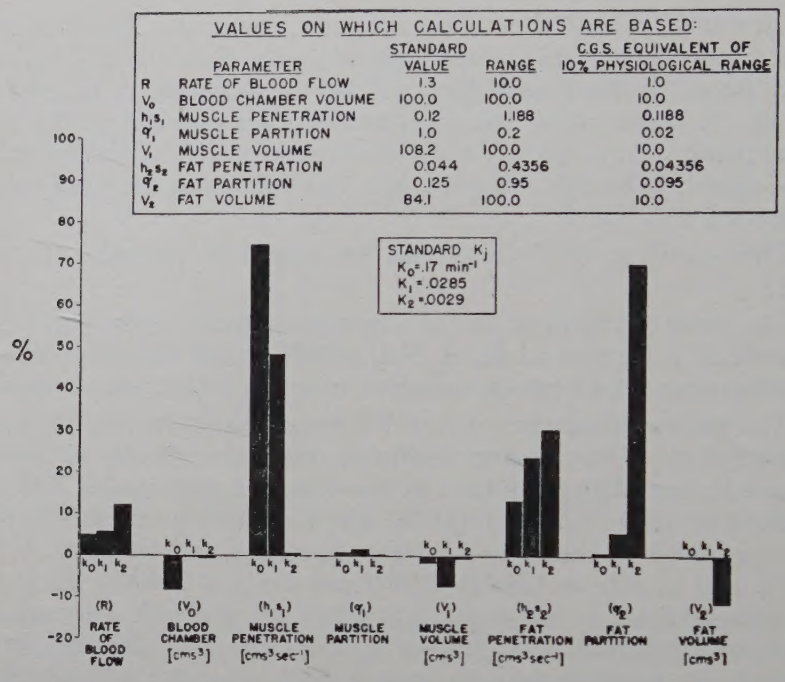

FIGURE 2

of subject C.J.S. (tabulated in Figure 2) are substituted into equation (3), we obtain,

$$k_j^3 - (3.37582 \times 10^{-3})\, k_j^2 + (1.519354 \times 10^{-6})\, k_j - (.06643 \times 10^{-9}) = 0\,,$$

whose graphical solution appears in Figure 3. On the other hand, when we substitute the values into the partial derivatives (4) and

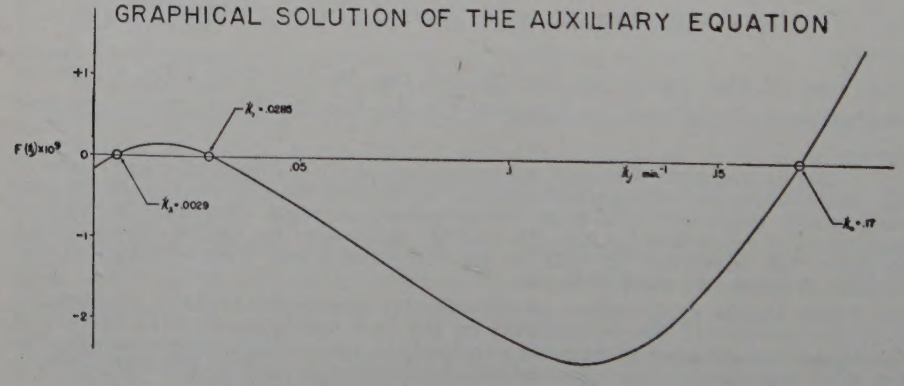

FIGURE 3

correct for range, we obtain the per cent changes (Figure 2) induced in the k_j (hence on the speed of exchange) by changes in the physiological state, *quod erat faciendum.*

Let us now see how justified we are in accepting our results by examining the comparison between experiment and independent prediction.

1. Since in calculating the k_j we have at least on two occasions been obliged to use values which were certain only up to an order of magnitude, we may reasonably require only that the theoretical and empirical decay constants agree up to an order of magnitude. This is certainly the case:[6]

	Empirical	Theoretical
k_0	.11	.17
k_1	.058	.03
k_2	.02	.003

We suppose that it would be improbable indeed that ten reasonable values assumed for ten independent quantities should yield reasonable answers by sheer accident.[7]

2. Not only is the theoretical form (exponential sum) the best fitting empirical expression, but also the predicted number of exponentials ($n + 1 = 2 + 1 = 3$) turns out empirically to be the best number.

3. It will appear below that the size, direction, and nature of the theoretically deduced partial derivatives is in good accord with what one would expect on physiological grounds and/or on the basis of experiment.

The three foregoing observations we have taken to favor the acceptance of our equation (1), and hence to warrant the consideration of the derivatives in Figure 2 as expressing approximately the effectiveness of various influences in governing the speed of inert gas exchange. Study of these derivatives permits the following remarks:

1. The early stages of absorption are governed chiefly by the state of the blood, the intercellular fluid, and the charactertstics of

[6] It has been customary in this field to express decay constants in min^{-1}; we have therefore converted from cgs units.

[7] Where comparison is possible our empirical values are well within the range obtained by others. Since the left member of equation (3) is continuous for $k_j \neq \pi_i$, we can be sure that normal deviations of physiological values from the standards we have assumed will lead to decay constants which themselves remain within the normal range. The interesting ordering relationship between the k_j and π_i has itself important applications (3, 5).

aqueous tissue (e.g., muscle), in the sense that these are the influences to which k_0 is most susceptible.

2. The later stages of absorption are governed chiefly by the interaction of the gas with fatty tissue. Thus the smaller the amount of fat, the greater the fat solubility, or the greater the fat permeability, then the more rapidly will the absorption be terminated, for these are the influences to which k_2 is most susceptible.

3. Both conclusions 1 and 2 can be reached without the untenable concept formerly held that each exponential was determined solely by the constant of one type of tissue.

4. Experimental procedures designed to affect one or another of the physiological parameters could eventually lead to a rather fine control of the absorption curve.

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CONTRIBUTION TO THE THEORY OF DISCRIMINATION LEARNING

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In the first two sections, which deal, respectively, with simple and double (or successive) discrimination, a comparison is made between the theory presented and certain experiments on time discrimination. Section III sets forth a possible theoretical approach to multiple choice discrimination.

I

In a discrimination problem in which there is a choice between a "correct" response and an "incorrect" response, we may designate the probability of a correct response being made on the n-th trial as $\alpha(n)$. In the experiments to be discussed in this section there is only one correct response and one incorrect response possible per trial. Also, $\alpha(0) = \frac{1}{2}$ because of the symmetry introduced. We are interested in the nature of the function $\alpha(n)$.

We introduce a more or less intuitive postulate whose justification will rest in the experimental verification of deductions made from it, rather than in an attempt to deduce it from more fundamental considerations. It may be remarked that the postulate will lead to an equation which is a special case of a more general equation obtained by H. D. Landahl (1941) from a considerably more detailed argument. However, the present very simple derivation may also be of some interest.

We postulate that the increase in the probability of a correct choice, as a result of additional experience, is proportional to the amount of improvement in this probability still possible and to the amount of additional experience. That is,

$$d\alpha = k(1 - \alpha)\,dn\,, \tag{1}$$

where k is a proportionality constant and is a function of the individual's aptitude and of the intrinsic difficulty of the experiment. Integrating equation (1) with $\alpha(0) = \frac{1}{2}$, we obtain

$$\alpha(n) = 1 - \tfrac{1}{2}\, e^{-kn}\,. \tag{2}$$

Now α is not an experimentally determinable quantity. The nearest we can come to it is the average number of correct responses made over a certain range in n. However, $E(n)$, the total number of errors made during n trials, is easily obtainable. We have

$$\frac{dE}{dn} = 1 - \alpha, \tag{3}$$

and

$$E = \int_0^n (1 - \alpha)\, dn. \tag{4}$$

Hence

$$E(n) = \frac{1}{2k}(1 - e^{-kn}). \tag{5}$$

This is a special case of H. D. Landahl's (1941) equation (34).

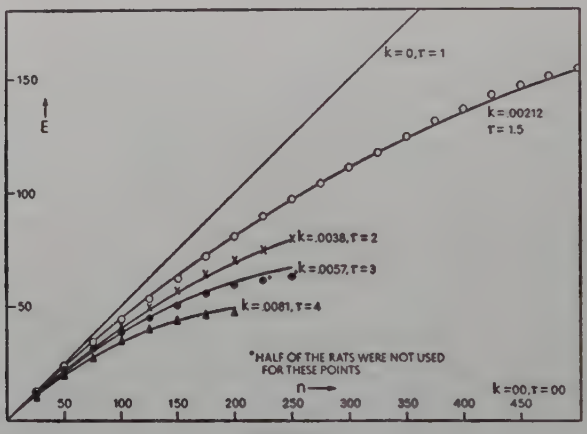

FIGURE 1

The nature of equation (5) is shown in Figure 1 for different values of the parameter k (smooth curves). Obviously, the line $E = \frac{1}{2}n$ corresponds to $k = 0$ and no discrimination, while the line $E = 0$ ($k = \infty$) holds for perfect discrimination from the outset.

A. C. Anderson (1932) conducted an extensive experiment on time discrimination in white rats in which each rat had to learn which of two doors was associated with a short detention period and which with a long detention period. Different differences and ratios of detention periods were used on different groups of rats in order to test Weber's law. It was found that Weber's law was indeed satisfied. That is, the average rate of learning was the same, within the random error to be expected for relatively small groups of rats, for

groups which had the same detention or discrimination *ratios* but different *differences*.

Four discrimination ratios were used by A. C. Anderson, $r = 4$, 3, 2 and 1.5, with 4, 16, 32 and 8 rats, respectively, as subjects for the different ratios. (The discrimination ratio r is defined as $r = t_l/t_s$, where t_l and t_s are the duration in seconds, say, of the long and short detention periods, respectively.) Average values of E were calculated from Anderson's data at intervals of $n = 25$ and these average values are plotted in Figure 1 against n. The smooth curves are theoretical curves, from equation (5), for the values of k specified in the figure. The points are experimental points. It can be seen that the agreement is quite good.

We now turn to a more detailed examination of the constant k, which may be called the discrimination coefficient. It is seen from equation (1) that the rate of learning is proportional to k. This coefficient may be considered a function of two quantities r and a, where r is the discrimination coefficient and a depends on the individual and the difficulty of the experiment (without regard to r). It is of considerable interest to discover the form of the function $k(a,r)$, since this would make it possible to express Weber's law quantitatively.

As we are using average scores in connection with the Anderson experiment, it may be expected that a is nearly the same for the different values of r (it would, of course, be advantageous to have larger numbers of animals). Hence, plotting $k(a,r)$ from the experimental data against r, as in Figure 2, should give approximately, at

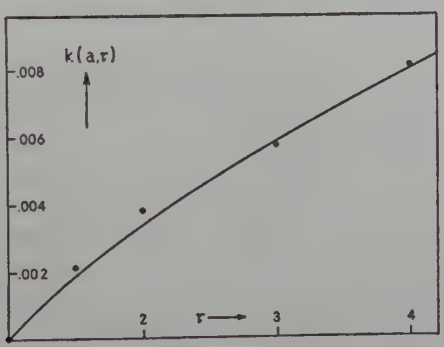

FIGURE 2

least, the type of dependence of k on r at constant a. No information is available on the variation of k with a.

Figure 2 suggests* that $k(a,r)$ may have the simple form

* We are indebted to Professor H. D. Landahl for pointing this out.

$k = a \log r$, which agrees with the quantitative formulation of Weber's law suggested by Fechner. Future and more detailed experiments and analysis are necessary to verify this, and to investigate the generality of this equation.

II

J. T. Cowles and J. L. Finan (1941) performed a time discrimination experiment on white rats in which a given rat was first detained in a chamber for either a short or a long period of time. On release, the rat was allowed the choice of two doors. One door was associated with the short time interval and one with the long. The "correct" response was to attempt to enter the door associated with the detention period used on the particular trial. The reward for a correct choice was an open door leading to food. Punishment for an incorrect choice was a blocked door, which necessitated, in order to reach food, a reversal of choice and a passage through the correct door. Cowles and Finan point out several faults in Anderson's experiment, as an experiment in pure time discrimination, and these faults are corrected by the procedure Cowles and Finan adopt. On the other hand, although it is true that the discrimination in the Anderson experiment is a sort of combined space-time discrimination, whatever type of discrimination it is, it involves only a *single* discrimination on the part of the animal, while the Cowles and Finan experiment is in reality a *double* discrimination problem. That is, in the Cowles and Finan case the rat is first faced with a pure time discrimination, but instead of the reward for a successful discrimination being food and the punishment an absence of food, the rat receives food in due course in either case. Hence, the reward is essentially a short path to food while the punishment is essentially a long path to food. Thus, in order for the rat to appreciate the reward he must be able to discriminate between the short and long paths (or time delays). This problem involves, then, a double discrimination: a temporal discrimination at the outset and then a spatial (or mixed spatial-temporal) discrimination in connection with the reward-punishment system. The object in this section will be to consider such a double discrimination problem from a theoretical point of view.

We shall derive the probability α that an animal will make the correct choice in the following problem: a primary discrimination problem is presented and then a choice of two alternatives; the two alternatives (reward, punishment) are not of an all-or-none character but involve a further discrimination. If the rat performs the first discrimination successfully he must also have discriminated previously between the reward and punishment in order to choose the

correct alternative with surety. As a good example of this sort of problem, one might vary with the Cowles and Finan experiment as follows. After the initial detention, both doors are left open but on passing through either door the rat is detained in a new chamber for a certain length of time before being released to food. A long detention period is punishment and a short detention period—reward. The reward-punishment system here would demand a discrimination of the type used by A. C. Anderson and by C. F. Sams and E. C. Tolman (1925).

Let α_1 be the probability that a correct choice would be made if only the first discrimination were necessary (i.e., with an all-or-none reward-punishment system). Let α_2 be the probability that a correct choice would be made if only the second discrimination were necessary (i.e., if the first "discrimination" were of an all-or-none character). Since α_1 and α_2 involve only single discriminations, the equations of Section I should hold with

$$\begin{aligned} \alpha_1 &= 1 - \tfrac{1}{2} e^{-k_1 n}, \\ \alpha_2 &= 1 - \tfrac{1}{2} e^{-k_2 n}. \end{aligned} \tag{6}$$

In equations (6)

$$\begin{aligned} k_1 &= k_1(a_1, r_1), \\ k_2 &= k_2(a_2, r_2), \end{aligned} \tag{7}$$

and

where r_1 and r_2 are the two discrimination ratios used. In the first case mentioned above α_1 is the probability of the correct choice being made but it is not the probability of the first discrimination being made, since even when the discrimination is not made the probability of making the correct choice is *equal* to the probability of making the incorcect choice. Therefore, if $\frac{1}{2}e^{-k_1 n}$ is the probability of an incorrect choice, twice this quantity, or $e^{-k_1 n}$, is the probability of the discrimination not being made and $1 - e^{-k_1 n}$, the probability of it being made. Now, if the first discrimination *has* been made the probability of making the correct choice in the presence of the second discrimination is α_2, and the probability of not making it is $1 - \alpha_2$. If the first discrimination *has not* been made, the probability of making the correct choice is $\frac{1}{2}$, regardless of α_2. Therefore, adding the two contributions to α and $1 - \alpha$,

$$\alpha = \alpha_2(1 - e^{-k_1 n}) + \tfrac{1}{2} e^{-k_1 n}, \tag{8}$$

and

$$1 - \alpha = (1 - \alpha_2)(1 - e^{-k_1 n}) + \tfrac{1}{2} e^{-k_1 n}. \tag{9}$$

Hence,

$$E = \int_0^n (1-\alpha)\,dn$$
$$= \frac{1}{2k_1}(1-e^{-k_1 n}) + \frac{1}{2k_2}(1-e^{-k_2 n}) \qquad (10)$$
$$- \frac{1}{2(k_1+k_2)}(1-e^{-(k_1+k_2)n}).$$

We may now return to the experiment of Cowles and Finan. The averages given by these authors for six rats at intervals of $n = 60$ are used in Figure 3. The dotted curve, which does not seem to fit

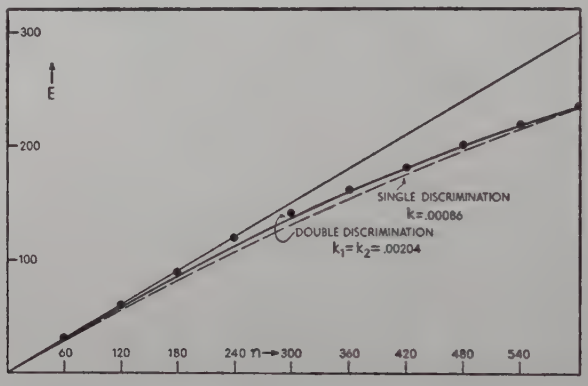

FIGURE 3

the experimental results, is based on the assumption of single discrimination [equation (5)]. This curve was chosen to pass through the last experimental point ($k = .00086$). Other choices would not lead to any better general agreement. The solid curve in Figure 3 is based on equation (10) and therefore assumes double discrimination. Quite arbitrarily, in the absence of other information, it was assumed that $k_1 = k_2$. The curve given is for $k_1 = k_2 = .00204$. Actually, the goodness of fit seems to be rather insensitive to the value chosen for k_1/k_2. In an experiment designed intentionally as a double discrimination experiment, k_1 and k_2 could be obtained independently by letting $r_2 \to \infty$ and $r_1 \to \infty$, respectively. Also, if $E(\infty)$ is obtained experimentally, this provides a relation between k_1 and k_2.

III

In this section a different type of generalization of equation (2) than that considered in Section II will be treated briefly. As far as

we are aware, data are not available at the present time for a comparison of the theory of this section with experiment.

Suppose that in a single discrimination problem there are N choices instead of two. Thus, in an experiment similar to the A. C. Anderson experiment, there might be three different detention periods, each associated with one of three doors (and detention chambers) placed in equivalent positions (at the vertices of an equilateral triangle). In part of Anderson's experiment four doors were actually used, but they were not placed in equivalent positions. In fact it is not possible to place four doors in equivalent positions in two dimensions, since there are three essentially different assignments of four different detention periods to the four corners of a square (there is only one such assignment for an equilateral triangle and three detention periods). Hence, for $N > 3$, experimental results would be somewhat questionable.

Let the detention periods (if the discrimination is time discrimination) be $t_1, t_2, \cdots, t_N$ in increasing order. Let α_i be the probability of the door associated with t_i being chosen. Clearly, when $n = 0$,

$$\alpha_1 = \alpha_2 = \cdots = \alpha_N = \frac{1}{N}, \tag{11}$$

and when $n = \infty$,

$$\alpha_1 = 1, \quad \alpha_2 = \alpha_3 = \cdots = \alpha_N = 0. \tag{12}$$

In this general case the correct response is the choice of D_1 (the door associated with t_1), and the choice of any other door is incorrect. We postulate here that equation (1) still holds in an appropriate form:

$$d\alpha_1 = k_1(1 - \alpha_1)\, dn. \tag{13}$$

From equations (11) and (13),

$$\alpha_1(n) = 1 - \frac{N-1}{N} e^{-k_1 n}. \tag{14}$$

The discrimination coefficient k_1 will be a function of $t_1, t_2, \cdots, t_N$.

Let $p_1 = \alpha_1$ be the probability of D_1 being chosen, p_2 be the probability of D_2 being chosen if D_1 is not chosen, p_3 be the probability of D_3 being chosen if D_1 and D_2 are not chosen, etc. Obviously $p_N = 1$ and

$$\alpha_i = p_i \prod_{j=1}^{i-1} (1 - p_j). \tag{15}$$

We now postulate further that

$$dp_i = k_i(1 - p_i)\, dn; \qquad 1 \leqq i \leqq N, \tag{16}$$

giving

$$p_i = 1 - \frac{N-i}{N-i+1} e^{-k_i n}; \quad 1 \leqq i \leqq N. \tag{17}$$

Equation (17) takes the view that if D_1, D_2, $\cdots$, and D_{i-1} are not chosen, the next most "correct" choice is D_i and hence p_i, by definition, should be of the same general form as $\alpha_1 = p_1$. The coefficient k_i is the same function of t_i, $\cdots$, t_N as k_1 is of t_1, $\cdots$, t_N.

We define the experimentally measurable quantity $S_i(n)$ as the total number of choices of D_i in n trials. Then

$$S_i(n) = \int_0^n \alpha_i(n)\, dn. \tag{18}$$

Substituting equations (15) and (17) into equation (18), one obtains on integration

$$S_1 = n - \frac{N-1}{N k_1}(1 - e^{-k_1 n});$$

$$S_i = \frac{N-i+1}{N(k_1 + \cdots + k_{i-1})}(1 - e^{-(k_1+\ldots+k_{i-1})n}) \quad i > 1 \tag{19}$$

$$- \frac{N-i}{N(k_1 + \cdots + k_i)}(1 - e^{-(k_1+\ldots+k_i)n}).$$

It would be of considerable interest to test these equations experimentally, especially in view of the fact that it is by no means certain that the set of postulates adopted here are the correct ones.

The above discussion uses time discrimination as an example but is, of course, not restricted to this type of discrimination.

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THE MATHEMATICAL BIOPHYSICS OF SOME MENTAL PHENOMENA

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In this paper some aspects of the mathematical biophysics of the central nervous system, which hitherto have not been treated, are discussed. First, a neurobiophysical mechanism for consciousness is suggested. It provides for the possibility of conscious and unconscious reactions. Next, a mechanism of memory, both on the conscious and subconscious level, is suggested. The gradual forgetting of remote events is ascribed to the inhibition of older memory traces by the more recent ones. On the average, an exponential decay of memory with time is thus obtained, although memory for unusually strong experiences follows a somewhat different law of decay. A homeostatic mechanism is then considered which regulates the level of accumulated excitation or inhibition. Such a mechanism, under certain disturbing conditions, will result in periodical fluctuations of the total cortical excitation with periods varying within a very wide range. Finally, a mechanism for foresight and desire of future events is suggested. The latter provides for the possibility of the formation of subconscious reactions and habits, which may be abolished by bringing them into consciousness.

The recent developments of mathematical biophysics have accounted for a large number of phenomena in the central nervous system, ranging from a quantitative description of reaction times to such complex phenomena as learning (Householder and Landahl, 1945). An approach to the problem of emotions through the study of the mechanism of pleasantness or unpleasantness of visual (Rashevsky, 1938a, b; 1940; 1942a, b; Rashevsky and Brown, 1944a, b) and acoustical (Rashevsky, 1941) stimuli has also led to correct prediction of new experimental results. The field of the theory of the central nervous system is, however, as broad and complicated as the manifoldness of the functions of the brain. In spite of having covered a very wide range of phenomena in this field, mathematical biophysics has still left out much more than it has covered. In the present paper we shall outline some approaches to important phenomena in the brain, which thus far have not received adequate treatment at the hand of the mathematical biophysicists.

We shall begin by considering neurobiophysical mechanisms which may throw some light on the nature of consciousness and memory.

Let a number of afferent fibers *I* (Figure 1) lead to the cortex and synapse each with a fiber *II*, as well as with the usual cross-inhibitory fibers *III*. For simplicity, not all of fibers *III* are shown in the Figure. The scheme thus far is similar to the one studied before (Rashevsky, 1938a, chap. xxii). If the stimulus pattern affecting the peripheral ends of fibers *I* is pleasant, then the same pattern will be duplicated in fibers *II* (Rashevsky, 1940, chap. xii). For unpleasant stimuli some or all of the fibers *II* will not be excited because an un-

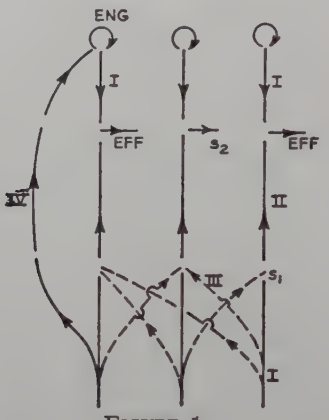

FIGURE 1

pleasant stimulus results in a net inhibition of the set of synapses s_1. Let, however, each fiber *I* send an excitatory fiber *IV* to a different cortical level in which it excites a self-circuiting neuron (Householder and Landahl, 1945) *Eng*, which has a low permanent excitation threshold, so that a moderate or even weak intensity of excitation E_{IV} of fiber *IV* throws it into a permanently excited state. Let each *Eng* send neurofibers *I'* downwards, so as to produce an excitation of the efferent neurons *Eff*, synapsing with *II* at s_2. With this arrangement even an unpleasant stimulus pattern results in an excitation of the efferent and of *II*, as should be the case. Without this or a similar arrangement we would be led to the absurd conclusion that an unpleasant stimulus pattern cannot produce any reaction at all. With the present mechanism there is, however, an essential difference between pleasant and unpleasant stimuli. In the case of the former ones, the efferent neurons *Eff* are activated both through *II* and through *Eng*, while in the latter case the *Eff* neurons are activated through *Eng* only. The biophysical correlate of unpleasantness is inhibition of neurons *II*.

Each *Eng* neuron provides a memory trace or engram of the corresponding stimulus, since *Eng* remains excited after the stimulus

subsides. At first glance, one might be inclined to assume that we perceive a stimulus pattern directly when the efferents *Eff* are excited through *II*, while we only remember a stimulus pattern if the afferent region is excited only through *Eng*. With this simple picture, however, a very unpleasant stimulus pattern which does not excite any neurons *II* would not be perceived as real at all, but only as a memory. This hardly corresponds to facts in general. However, this may have something to do with the feeling of unreality which a very painful situation produces in some individuals.

We now complicate the picture by having excitatory fibers, perhaps rather weak ones, connect each neuron *I* with the corresponding efferent neuron *Eff*, by-passing the corresponding neuron *II*. The total excitation or inhibition of the neurons *II* still remain the measures of pleasantness or unpleasantness, but even the most painful situation will now give a feeling of reality because it will have excited the neurons *Eff* not through *Eng* only.

With this mechanism the memory of an unpleasant event is in no way different from that of a pleasant event. Neither memory involves neurons *II*. This in itself does not necessarily contradict any observations. We frequently think without particular pain of past events which at the time of their occurrence were extremely unpleasant. However, sometimes memories themselves are very painful. To account for this we must complicate somewhat our neural mechanism.

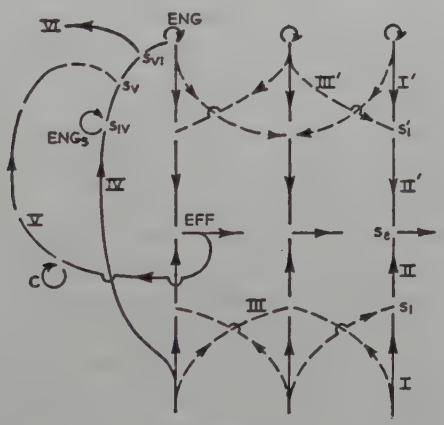

FIGURE 2

Let each *Eng* (Figure 2) send "down" a fiber *I'*, synapsing at s'_1 with a fiber *II'*, which in its turn synapses at s_e with the same efferent neuron as the corresponding neuron *II*. Let each *I'* send cross-inhibitory fibers *III'* to each s'_1, so as to form a sort of mirror image

of the system of neurons *I* and *II*. Let, moreover, each neuron *I* and each neuron *I'* send excitatory fibers to the corresponding efferents, by-passing neurons *II* and *II'* correspondingly.

A directly perceived stimulus pattern is pleasant if it results in the excitation of neurons *II* and *II'*. A directly perceived stimulus pattern is unpleasant if it results in an inhibition of both neurons *II* and *II'*. A memory of a pleasant stimulus pattern exists when neurons *II'*, but not *II* are excited, while a memory of an unpleasant pattern exists when neurons *II* and *III* are not excited at all, but neurons *II'* and *III'* are excited in such a way that the net result is an inhibition at the synapse s'_1.

In general, the memory of a pleasant event will be less pleasant than the event itself, since only neurons *II'*, instead of both *II'* and *II*, are excited and excite neurons *Eff*. The memory of an unpleasant event is less unpleasant than the event itself. This seems to agree with observations.

Events of which we are conscious we do usually remember to a greater or lesser degree. We speak of an unconscious act, if we do not ordinarily remember it. This suggests that the excitation of the *Eng* neurons corresponds to consciousness of an event.

If the synaptic delay along fibers *IV*, each of which may actually be a chain of fibers, is long, then some stimulus patterns may produce a reaction through the neurons *Eff*, *before* the neurons *Eng* are stimulated. Such a reaction is subconscious and is not consciously remembered. If each of the efferent neurons *Eff* sends an inhibitory fiber *V* to one of the synapses of the corresponding chain of fibers *IV*, then once such a subconscious reaction is produced, before the corresponding neuron *Eng* is excited, a subsequent excitement of that neuron *Eng* will be prevented. The act remains subconscious. In the absence of such an additional mechanism, or when the reaction is short, and therefore the inhibition of the chains *IV* is short, the neurons *Eng* may be stimulated after the corresponding efferent neurons. Thus we may or may not remember afterwards an act of which we were not conscious at the time of its performance.

It is, however, known that subconscious acts may in a way be remembered also, though the memory itself is on the subconscious level. Under the action of some drugs, such as sodium amital, such "subconscious" memories may be evoked. The above picture does not account for that, and we must complicate it further.

Let each of the fibers *V* be a chain of fibers, and let that chain at some place s_{IV} synapse with a self-circulated neuron Eng_s. Let each of the chains of fibers *V*, mentioned above, inhibit through a last inhibitory link a synapse of the chain *IV* somewhere between Eng_s and

Eng. Let, moreover, the chain of fibers *V* have at one of its synapses a self-circuited circuit *C*, whose permanent excitation threshold is such that when *V* is excited weakly the excitation is reversible, but when *V* is excited strongly, the circuit is excited permanently and the part of the chain *V* between the circuit and s_V (Figure 2) remains permanently excited.

With this mechanism, once a sufficiently strong subconscious reaction is produced, the corresponding Eng_s are excited but not the corresponding neurons *Eng*. This may be interpreted as meaning that the individual will not consciously remember the event but it will be stored in the subconscious memory. If through the action of some factor, for example sodium amital, the chain *V* between *C* and s_V is inhibited, the excitation of Eng_s causes an excitation of *Eng*, and the event is remembered.

The individual's reaction to such a "disinhibited" previously subconscious memory will be through *Eng*, I', s'_1, and II'. In this case, once a subsconscious memory is evoked into consciousness, it remains conscious. The chain *IV* may, however, branch off at s_{VI} an excitation chain *VI* which connects directly to *Eff*. In that case, disinhibition of s_V may produce a reaction through *VI* and *Eff*, without necessarily exciting the neurons *Eng*. The reaction may be interpreted as the individual's statement about a past event remembered only subconsciously. But when the disinhibition is over and the neurons *Eng* did not become excited, the individual will again not remember the event. All will depend on the intensity of excitation of Eng_s or of the intensity of excitation E_{IV} of the neuron chain between Eng_s and *Eng*. If E_{IV} is greater than the threshold h^* of the permanent excitation of *Eng*, the inhibition of *V* will result in a conscious memory of the event, even after the disinhibition is over. Otherwise, the individual will again forget consciously the event.

It is empirically known that memory of an event becomes weaker as time goes on. One might attempt to interpret that in terms of a gradual extinction of the excitation of the engramic neuron. Such an interpretation meets, however, with a fundamental biophysical difficulty. The time factors for all kinds of processes in single neurons are of the order of small fractions of a second. Memories, on the other hand, may last for years. Hence we would have to introduce *ad hoc* some very slow process as an additional hypothesis. Invoking in this case the possibility of very slow somatic changes does not seem plausible. The following scheme takes care of the situation in a much more natural way, without any additional assumptions beyond those usually made in the mathematical biophysics of the central nervous system.

Let each engramic neuron *Eng* send to every other one inhibitory fibers. In the stream of experience more and more engrams become excited. Hence each of the already excited engrams becomes more and more inhibited by the others. The memory for any event will gradually weaken because of inhibition by memories of new events. Thus a general weakening of memory will occur, as time goes on. But this weakening, contrary to facts, would affect equally the recent and the long past memories. Only the strongest memories will eventually remain, the weaker ones being completely inhibited.

The network shown in Figure 2 provides for such a mechanism, though in a too restricted sense. According to Figure 2, we should not remember too complex situations, or remember several things at one time, for all involved engrams will become inhibited when their number exceeds a critical value n^* (Rashevsky, 1938a, chap. xxii). With such a scheme we would find that if on the average a constant number of engrams are formed per unit time in the stream of experience, then after a finite time all engrams will become inhibited and no memory will be possible.

A different mechanism is provided by cross-inhibitory fibers going from synapse to synapse (Rashevsky, 1938a, chap. xxii, Figure 56), as shown on Figure 3.

FIGURE 3

Let E be the excitation of each engram. For simplicity we now assume E to be the same for all of them. In the stationary state the value of ε produced at the synapse is, using previous notations (Rashevsky, 1938a),

$$\varepsilon = \frac{A}{a} E = \gamma E. \tag{1}$$

Denoting by h the threshold of the cross-inhibitory fibers, we find that the excitation E_i of each of the inhibitory fibers is

$$E_i = \beta(\varepsilon - j - h), \tag{2}$$

where j is the total amount of inhibitory factor at the synapse, while the amount of inhibitory factor produced by each inhibitory fiber is

$$j^* = \frac{B}{b} E_i = \gamma_1 E_i. \tag{3}$$

Equations (2) and (3) give

$$j^* = \beta\,\gamma_1(\varepsilon - j - h). \tag{4}$$

If the total number of excited engrams is n, then at each synapse

$$j = (n-1)\,j^* = \beta\,\gamma_1(n-1)\,(\varepsilon - j - h). \tag{5}$$

Putting

$$\varepsilon - j = \phi, \tag{6}$$

we have from equations (1) and (5)

$$\phi = \gamma\,E - \beta\,\gamma_1(n-1)\,(\phi - h), \tag{7}$$

which gives

$$\phi = \frac{\gamma\,E}{1+\beta\,\gamma_1(n-1)} + \frac{\beta\,\gamma_1(n-1)}{1+\beta\,\gamma_1(n-1)}\,h. \tag{8}$$

For any finite n the excitation ϕ is positive, and tends to h as n becomes infinite. If the threshold h is very small, we may neglect the second term of the right side of equation (8) and obtain

$$\phi = \frac{\gamma\,E}{1+\beta\,\gamma_1(n-1)}. \tag{9}$$

Since n varies linearly with time, therefore ϕ tends to zero as $1/t$.

If one engram is excited with the intensity E_1 and the other $(n-1)$ engrams with intensities $E_2 < E_1$, then we have, neglecting h,

$$\begin{gathered} \varepsilon_1 = \gamma\,E_1, \qquad \varepsilon_2 = \gamma\,E_2; \\ j_1 = \beta\,\gamma_1(n-1)\,\phi_2; \qquad j_2 = \beta\,\gamma_1(n-2)\,\phi_2 + \beta\,\gamma_1\,\phi_1. \end{gathered} \tag{10}$$

Hence with

$$\beta\,\gamma_1 = \eta, \tag{11}$$

we have

$$\begin{aligned} \phi_1 &= \gamma\,E_1 - \eta(n-1)\,\phi_2; \\ \phi_2 &= \gamma\,E_2 - \eta(n-2)\,\phi_2 - \eta\,\phi_1. \end{aligned} \tag{12}$$

This gives

$$\phi_1 = \frac{\gamma\,E_1 + \gamma\,\eta(n-2)\,E_1 - \gamma\,\eta(n-1)\,E_2}{(1-\eta)^2 + \eta(1-\eta)\,n}; \tag{13}$$

$$\phi_2 = \frac{\gamma\,E_2 - \gamma\,\eta\,E_1}{(1-\eta)^2 + \eta(1-\eta)\,n}. \tag{14}$$

For $E_1 = E_2$ those equations reduce to expression (9).

If E_1 and E_2 are of the same order of magnitude, then for ϕ^1 and ϕ_2 to be positive we must have $\eta << 1$. If $\eta << 1$ and $E_1/E_2 > 1/\eta$, then $\phi_2 < 0$. Physically this means that none of the inhibitory fibers converging on the engram with excitation E_2 are excited. Hence in that case $\phi_1 = \alpha E_1$. Again only the strongest engram is excited at all, the others being inhibited.

The above mechanism results in a weakening of memories with time, the weakening being the same for recent and long past events. Actually, recent events are remembered better than old ones, other conditions being equal. This suggests that while newly formed engrams inhibit those formed previously, they themselves are not inhibited, at least appreciably, by those previous ones.

The following mechanism provides for such a situation. Let any two engrams be connected as represented on Figure 4. Let the inhibitory 12′ and 21′ be of the same strength as the excitatory fibers 12, and 21. If I is excited first, then 12 and 12′ will cancel each other

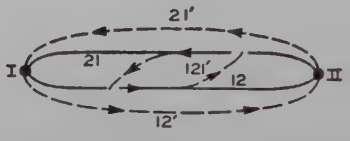

FIGURE 4

out and II will not be inhibited. But if after that II is excited, then I will be inhibited via 21′ because 21 is inhibited by the previous excitation of 121′. The constants of 121 must be such that 121 is excited strongly even by weak stimuli, so that when the excitation of I is reduced through inhibition by II, still 121 would inhibit 21. Due to the symmetry of the arrangement, if II is excited before I, II will be affected by I, but not I by II.

Consider now n engrams all excited at different times. Denote by 1 the engram which is the last to be excited; by 2 the one before last, and so on. Let their intrinsic intensities of excitation be all the same and equal to E. Then for the first engram, we have

$$\phi_1 = \alpha E, \tag{15}$$

since it is not inhibited by any others. For the second we have, neglecting the threshold of the inhibitory fibers,

$$\phi_2 = \alpha E - \eta \phi_1 = \alpha E (1 - \eta). \tag{16}$$

For the third we have

$$\phi_3 = \alpha E - \eta (\phi_1 + \phi_2) = \alpha E (1 - 2\eta + \eta^2) = \alpha E (1 - \eta)^2. \tag{17}$$

If

$$\phi_n = \alpha E (1-\eta)^{n-1}, \tag{18}$$

then

$$\begin{aligned} \phi_{n+1} &= \alpha E - \eta(\phi_1 + \phi_2 \cdots \phi_n) \\ &= \alpha E\{1-\eta[1 + (1-\eta) + (1-\eta)^2 + \cdots + (1-\eta)^{n-1}]\} \\ &= \alpha E\left\{1 + \eta \frac{(1-\eta)^n - 1}{\eta}\right\} = \alpha E (1-\eta)^n. \end{aligned} \tag{19}$$

Since equation (18) holds for $n = 1$ and 2, it holds for any n. If n is proportional to the time t, then we have

$$\phi_t = A(1-\eta)^{Bt}, \tag{20}$$

which, since $0 < \eta < 0$, is a decreasing function of t. Thus the longer ago the engram was formed, the weaker it is. If at some time an engram is formed with an intensity $E^* > E$, and followed by $n-1$ engrams of intensity E, then

$$\begin{aligned} &\phi_n = \alpha E^* - \eta(\phi_1 + \phi_2 + \cdots + \phi_{n-1}) = \\ &\alpha E^* - \alpha E \eta[1 + (1-\eta) + \cdots + (1-\eta)^{n-2}] = \\ &\alpha E^* - \alpha E[1 - (1-\eta)^{n-1}]. \end{aligned} \tag{21}$$

As n increases and as time goes on, ϕ_n decreases but tends to a constant value $\alpha(E^* - E)$. Thus a few strong memories outstanding in the stream of experience will slightly decrease, but then remain constant. Of course all engrams are of different intensities, but we may consider them as of an average same intensity E, except for a few outstanding memories. If on the average outstanding memories will occur ever so often, then their intensity will also decrease with time to zero, since as time goes on their number mounts to infinity.

From the discrete case we may pass to the continuous and write, counting t backwards,

$$\phi(t) = \alpha E(t) - \eta \int_0^t \phi(\xi)\, d\xi. \tag{22}$$

Differentiating, and denoting

$$\frac{dE}{dt} = E', \tag{23}$$

we find

$$\frac{d\phi}{dt} = \alpha E'(t) - \eta\phi. \tag{24}$$

The general solution of equation (24) is

$$\phi = e^{-\eta t} \{\phi_0 + \eta \int_0^t E'(t)\, e^{\eta t}\, dt\}\,. \tag{25}$$

If $E(t) = \text{const.}$, then $E'(t) = 0$ and equation (25) gives

$$\phi = \phi_0\, e^{-\eta t}\,, \tag{26}$$

where ϕ_0 is the intensity of memory just formed.

We shall assume here that the above discussed mechanism of memory extinction holds only for the "conscious" memory. We shall consider that the neurons Eng_s do not cross-inhibit each other, and that therefore subconsciously even the remotest events may be remembered. The number of events stored in the subconscious is limited only by the total number of neurons Eng_s available.

In the stream of experience there is a constant increase of excitation on the level of neurons Eng_s. There is thus an accumulation of the level of the total net excitation $\phi = \varepsilon - j$ in the cortex. It is natural to assume some homeostatic mechanism which will tend to maintain a constant level ϕ_0. One of the simplest mechanisms of that kind would be the following (Figure 5). The impulses coming from

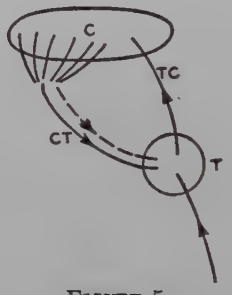

FIGURE 5

the external world are relayed to the cortex C through the thalamus T. While we may consider that in an ordinary stream of experience not upset by any too unusual events, the *average* flow of impulses to the thalamus will be constant, yet even then the intensity S of the individual impulses will be scattered around the average according to some distribution function $E(S)$. Let all the Eng_s neurons of C send fibers to the fibers CT (Figure 5), which are a pair of fibers, one excitatory, the other inhibitory. Since ordinarily the changes in the flow of outside stimuli are slow compared with the time constants of the neurons, we may consider the fibers CT as always in a quasi-stationary state of excitation.

The constants of the two fibers may be chosen so that for weak stimuli at C the excitatory fiber has almost reached its saturation

value, while the inhibitory one is only weakly excited. For strong stimuli the excitation of the inhibitory fiber catches up with that of the excitatory, and eventually exceeds it.

But then for high values of the total amount of $\phi_1 = \phi - \phi_0$ accumulated over a long period of time, the pair CT will act as an inhibitory fiber, raising the thresholds of the fibers TC, running from the thalamus to the cortex, and thus cutting off from the cortex some of the weaker stimuli of the stream of experience. This will result in a decrease of the rate of accumulation $d\phi_1/dt$. If the average rate of accumulation of ϕ_1, that is, the flow of stimuli is constant and equal to S_0, then we have, denoting by a and λ two constants of proportionality,

$$\frac{d\phi_1}{dt} = aS_0 - \lambda \int_{-\infty}^{t} \phi_1 dt. \tag{27}$$

By differentiation we obtain from equation (27)

$$\frac{d^2\phi_1}{dt^2} = -\lambda \phi_1, \tag{28}$$

the solution of which represents undamped harmonic oscillations within a period

$$T = \frac{2\pi}{\sqrt{\lambda}}. \tag{29}$$

In this simple case we would thus have periodical fluctuations of cortical excitation and inhibition. Unless at some time a particularly high value of S_0 has brought ϕ_1 to a very high value, the amplitude of the oscillations of ϕ_1 will be usually small. But if an external very strong experience has made ϕ_1 very large, the amplitude may become very large, and abnormally strong fluctuations of the state of excitation of the cortex will result, such as are observed in manic-depressive psychoses.

Let us consider the somewhat more general case when S_0 is not constant but is itself a function $S_0(t)$ of time. Then instead of equation (28) we shall have, putting $dS_0/dt = S_0'(t)$,

$$\frac{d^2\phi_1}{dt^2} + \lambda \phi_1 = aS_0'(t). \tag{30}$$

Let in general S_0 be constant, except for a short time when it rapidly raises to some value S_{01}, then after an interval of time T_0 again drops to the original constant value. The quantity S_0' then will raise from zero to a maximum value, drop again to zero, become negative, and

again return to zero. It will be represented by a curve as that shown in Figure 6. But then for that interval of time, equation (30) represents a forced harmonic oscillation. If T_0 is very close to $2\pi/\sqrt{\lambda}$, then even one "wave" of the external force, $S_0'(t)$, may increase the

FIGURE 6

amplitude of ϕ_1 very appreciably. An equal temporary increase of S_0 to the value S_{01} but for a period T_i which is much different from $2\pi/\sqrt{\lambda}$ will not result in such abnormally high amplitudes. It must be noted that bringing by some external means ϕ_1 and even S_0 to zero at some moment does not necessarily result in the cessation of the fluctuations because $d\phi_1/dt$ may remain at that moment either strongly positive or negative, depending on the value of the integral $\int_{-\infty}^{t} \phi_1 dt$.

Equation (27) should of course be considered only as a first approximation. The relation between $d\phi_1/dt$ and the cumulative value of ϕ_1 will in general be non-linear. The additional of non-linear terms will introduce harmonics into the oscillations and the possibility of periodical very sudden changes in ϕ_1 will be present.

If we consider another more general case, namely that the Eng_s neurons inhibit each other, or that the Eng neurons also connect with CT, then in the cumulative effect the amount of ϕ_1 which corresponds to a more remote time, contributes less than a recent ϕ_1. If we assume an exponential decay, as in equation (26), then instead of equation (27) we obtain, for a constant S_0,

$$\frac{d\phi_1}{dt} = aS_0 - \lambda \int_{-\infty}^{t} \phi_1(\tau)\, e^{-\eta(t-\tau)}\, d\tau. \tag{31}$$

Bringing $e^{-\eta t}$ outside of the sign of the integral, multiplying by $e^{\eta t}$, differentiating with respect to t, and then cancelling $e^{-\eta t}$, we obtain

$$\frac{d^2\phi_1}{dt^2} + \eta \frac{d\phi_1}{dt} + \lambda\, \phi_1 = a\, \eta\, S_0, \tag{32}$$

which represents damped harmonic oscillations, the amplitude decreasing as $e^{-\eta t}$. The greater η, in other words, the weaker the memory, the more rapidly the oscillations will die down. The value of ϕ_1 oscillates now not around $\phi_1 = 0$, $(\phi = \phi_0)$, but around $\phi_1' = a\, \eta\, S_0/\lambda$.

The neurobiophysical mechanisms discussed above provide for aftereffects of past experiences through memory. We now shall briefly discuss mechanisms which will have to be studied for the interpretation of the effects of anticipation of future events upon the individual. Fundamentally, any idea of a future event presupposes that the different elements of that event have been experienced in the past. The *combinations* of those elements may be entirely new, and never experienced before. But the elements themselves must have been given by previous experience.

It is natural to consider a generalization of the scheme of Figure 2, in which case each neuron *Eng* excites a fiber (Figure 7, VII) lead-

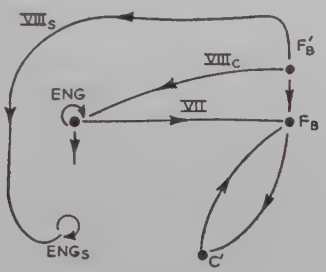

FIGURE 7

ing to a neuron F in some different region of the brain. While the excitation of an *Eng* neuron corresponds to a memory of a past event, a similar excitation of a neuron F corresponds to the idea of the event happening in the future. Since according to that scheme, a present event also excites the corresponding F neuron, we may use the following interpretation:

An event is perceived directly when the corresponding peripheral afferents, the *Eng* and F, are excited. If only *Eng* and F are excited, we have the memory of the event. If only F is excited, we think of the event in the future.

If in the past an experience A has been followed several times by the experience B, then the temporal pattern $A \rightarrow B$ will be "remembered" through the corresponding neurons *Eng*. During the experiencing of the temporal pattern $A \rightarrow B$, the corresponding neurons (or perhaps better, groups of neurons) F_A and F_B will also be excited. If the different neurons F are connected through "conditioning" pathways, discussed elsewhere, (Rashevsky, 1938a, chap. xxv; Householder and Landahl, 1945, chap. xi), then a simultaneous or closely successive excitation of F_A and F_B will have as a result that excitation of F_A alone will, through the conditioning pathway, elicit the excitation of F_B.

Let now experience A happen alone. Through the corresponding neuron *Eng* it will produce the excitation of F_A. Through previous conditioning F_B will become excited. But there will be no excitation of either the peripheral afferents nor will there necessarily be a very strong excitation of the *Eng* corresponding to the event B. Hence, the occurrence of A will make us *anticipate* B *in the future.* We have here an elementary mechanism of foresight.

Such phenomena as rational problem solving or planning are probably closely connected with the functioning of neurons F, involving mechanisms outlined elsewhere (Rashevsky, 1938a, chap. xxix).

When an external event evokes our concern or thought of a future event, it is frequently in the biological interest of the individual to concentrate on that future event for a sufficient time. A mechanism for such a concentration may be provided by the scheme shown in Figure 7. A neuron F excites some other center C', which in its turn excites F. This enhances the excitation of F. With properly chosen constants of the neurons involved, the circuit F_BC' will not remain excited if the original excitation of F is removed. But if in a pathological individual the constants of the circuit are different, then even the removal of the original stimulus A, which resulted in the excitation of F_B will leave the circuit F_BC', and hence F_B, excited. The individual will not be able to bring to a stop his concern about the future event F_B. If, as is natural to assume in accordance with the general mathematical biophysics of the central nervous system, each F sends inhibitory fibers to other parts of the brain, such a strong excitation of one group of F neurons will result in an inhibition of other functions of the central nervous system. Such a general inhibition may be removed by cutting the circuit F_BC'.

It is plausible to assume that the F neurons are located in the frontal lobes. It may be suggested that what is achieved in prefrontal lobotomy is just the severing of the circuits F_BC'. Once those circuits are destroyed, not only does the permanent preoccupation with one idea cease, but it becomes impossible for an individual to properly *concentrate* on future events. Complaints of lobotomised patients about a certain "haziness" of the future have been occasionally recorded in the literature.

Let a pattern $A + B$ be several times followed by a stimulus C_1 which produces the reaction R_1. Let, however, A alone not be followed by C_1. As a part of the pattern $A + B$, A will continually produce reaction R_1. Let A, presented alone, be followed by a stimulus C_2 which unconditionally produces the reaction R_2. While A is experienced alone several times, it not only becomes conditioned to R_2, but (Rashevsky, 1938a, chap. xxv) through it inhibits its own con-

nection with R_1. With properly chosen constants of the fibers, the process of extinction of the conditioned reflex $A \rightarrow R_1$ is slow. Moreover, after a period of rest when A was not experienced at all, an experiencing of A will again result in the reaction R_1 until A has been repeated alone a sufficient number of times. Hence in general, an experience of A will produce both R_1 and R_2. If the efferent paths of R_1 and R_2 cross-inhibit each other, only one of the reactions will be produced, namely the stronger one.

If B has been always followed by C_1 while A alone has been always followed by C_2, then we may say that reaction R_1 is the "correct" reaction to B, while the reaction R_2 is the "correct" reaction to A alone. The experience A may have occurred several times in conjunction with B accidentally, and thus become conditioned to R_1. If $A \rightarrow R_1$ has been very strong, $A \rightarrow R_2$ will not overcome it, and A will always result in the wrong reaction. If, in the pattern $A + B$, the central neurons, which form the beginnings of the conditioned circuits, cross-inhibit each other, then the conditioning of A to R_1 when in conjunction with B is weaker than if A were alone; for that reason the reaction $A \rightarrow R_1$ will be weaker than $A \rightarrow R_2$. Hence when A is presented alone, it will elicit the correct reaction R_2.

But if the cross-inhibition between A and B is weak, the reflex $A \rightarrow R_1$ may become so strong as to always prevail over $A \rightarrow R_2$.

Let A stand for the experience by a person of seeing another individual, and let B stand for this individual's performance of some hostile act. R_1 may then be a fright reaction, or the feeling that the other individual hates the person. On the contrary, R_2 may be a reaction of friendliness. If we always have $A \rightarrow R_1$, then the person has the feeling that every other individual is hostile to him or her. As follows from the above, this type of paranoia may be caused by too weak cross-inhibitory fibers between the afferent neurons.

The same situation may, however, be caused by an entirely different mechanism. Let R_1 be a very unpleasant reaction which results in a general cortical inhibition. Then if we first have $A + B \rightarrow R_1$ with a resulting $A \rightarrow R_1$, the process of conditioning of A alone to R_2 is inhibited because before the conditioned reaction $A \rightarrow R_2$ is established, the already existing reaction $A \rightarrow R_1$ produces inhibitions of all centers.

If, in particular, we assume that any unpleasant situation results in an excitation of a definite "pain" center which sends off inhibitory fibers to other parts of the brain, then the above discussed situation may be remedied by cutting the fibers leading from the rest of the cortex to the pain center. A surgical treatment of some paranoid conditions thus appears as a possibility.

As we have seen, qualitatively the same type of paranoid symptoms may be due to entirely different mechanisms. The next problem is to develop the different *quantitative* aspects of the two mechanisms by means already used in mathematical biophysics. In this way through *quantitative tests* it may be possible to establish which of the possible mechanisms is operating in a given case. This would have both diagnostic value as well as give clues to possible therapeutic procedure.

Let it be possible to condition Eng_s to any reaction, and let the *Eng*'s send inhibitory fibers to *all* conditioned pathways going from the corresponding Eng_s's. Then the mere bringing into consciousness of any subconsciously remembered event may abolish some subconsciously formed undesirable reaction.

Let now F_B be excited by a center F_B', which also is connected with both the corresponding *Eng* and Eng_s by tracts $VIII_c$ and $VIII_s$. The excitation of F_B' may be interpreted as corresponding to the desire of B. Due to the type of connections shown in Figure 7, when we desire B, we also *ipso facto* think of B in the future. But we may think of B in the future (excitation of F_B) without desiring it.

Suppose at some time the desire for B was followed by an event A, which produces reaction R. Since F_B' through $VIII_c$ and $VIII_s$ excites both *Eng* and Eng_s, either of which can be conditioned to produce R, R will be produced later on whenever the desire for B is experienced. If the excitation E_{VIII_c} of $VIII_c$ is always stronger than E_{VIII_s} of $VIII_s$, then the "subconscious" part of the conditioning, that is, the conditioning of Eng_s to B, will be inhibited by the excitation of the corresponding *Eng*. Thus the reaction R will be produced quite consciously, and if it is an undesirable reaction, it may be consciously suppressed. But if in an individual the connection $VIII_c$ is always much weaker than $VIII_s$, then the reaction R will be produced subconsciously. Reaction R may be undesirable, even antisocial, or even painful to the individual. Thus B may be attention by others, while A may be some physiological disturbance or mild illness producing the reaction R, say a headache or other symptom. If desire for attention (B) has been accidently followed immediately by A, and thus produced R, R may be produced again every time B is desired, although A (the actual physiological disturbance) may be absent. We have here a mechanism that produces some simple forms of hysteria. A hysterical individual, according to that picture, is characterized by $E_{VIII_c} < E_{VIII_s}$.

From this point of view, severing of $VIII_s$ may abolish some types of psychoneurotic behavior. In this connection it may be inter-

esting to speculate concerning the mechanism of the beneficial effects of prefrontal lobotomy. If all connections to and from the frontal lobes are severed, this would mean severing *VIII* , as well as the circuit $F_B - C'$ (Figure 7). The severance of the latter would, as mentioned above, abolish some types of depressions connected with constant concern over the future. Severance of $VIII_s$ would abolish certain types of hysterical behavior and subconscious habits. It may be worth noticing that improvements in psychoneurotics have sometimes been reported after lobotomy. Perhaps with further experimental study and improvement of surgical technique, it may be possible to sever at will either $VIII_s$ or circuit $F_B - C'$. Different kinds of "partial" lobotomies may perhaps be used in the future for different types of mental disorders. That a complete severance of *all* connections may not be necessary, seems to be indicated by some recent work (Hofstatter et al., 1945).

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BULLETIN OF
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MATHEMATICAL BIOPHYSICS OF ABSTRACTION AND LOGICAL THINKING

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Developing further a recent suggestion of H. D. Landahl, equations are derived which give the probability for an individual to judge two stimulus patterns as similar or dissimilar. The possibility of experimental verification of those equations is discussed. Next, a mechanism is described which provided for abstraction by responding only to "essential" components of a stimulus pattern. Equations, verifiable in principle experimentally, are derived. Finally, a mechanism is suggested for logical inferences, and equations are derived which give the probability of making an error in a reasoning consisting of a chain of syllogisms, as well as the probability of being unable to complete the chain of reasoning at all.

Recently H. D. Landahl (1945) has suggested a neurobiophysical mechanism which provides for the reaction of judgment of similarity and dissimilarity of two multimodal stimulus patterns, or in common parlance, of two objects. He suggested some applications to pathological cases of erroneous identification and confusion. The purpose of the present paper is to develop H. D. Landahl's suggestion further and to discuss a similar mechanism which provides for abstraction and for some forms of logical thinking. We presuppose the reader's familiarity with H. D. Landahl's paper.

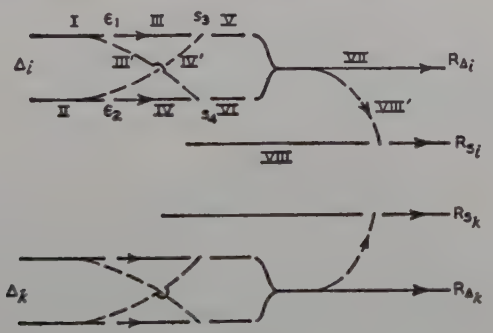

FIGURE 1

We first shall somewhat simplify H. D. Landahl's mechanism for perception of similarity. Let a mechanism A (Figure 1) for percep-

tion of differences in one modality, such as suggested by H. D Landahl, inhibit through the fiber *VIII'* a synapse of a chain of fibers VIII, which produce a reaction R_s, the similarity or identity reaction. The chain *VIII* may either be excited by a permanent self-exciting center or, what is more natural, may be excited by either of the two stimuli acting on the "difference mechanism". In this case, if the difference $\Delta_i = 0$, then no "difference reaction" R_Δ is produced, but the similarity reaction R_s is produced. If $\Delta_i > 0$, then R_Δ is produced, but R_s is absent.

According to this mechanism, similarity is a purely negative concept meaning absence of difference. A situation, mentioned by H. D. Landahl, that two things may be neither similar nor different, may occur with the present mechanism also, if the chain of fibers *VIII* is broken or inhibited somewhere between the synapse s_5 and the final path. Such a situation would, however, be pathological, whereas with Landahl's mechanism it may occur normally.

We now shall compute the probability p judgment of similarity in terms of Δ_i. The probability q of a judgment of difference is simply

$$q = 1 - p . \tag{1}$$

It follows from H. D. Landahl's discussion (1945) that the probability p is the same as the probability of a "doubtful judgment" in the mechanism for psychophysical discrimination studied by H. D. Landahl previously (1938). We may take over directly some of the equations developed by Landahl (1938). Since our Δ_i is essentially the same as $\varepsilon_1 - \varepsilon_2$ of Landahl (1938), we have, assuming a distribution function $p(\xi)$ for the fluctuation of excitation of the form

$$p(\xi) = \frac{k}{2} e^{-k|\xi|}, \tag{2}$$

the following expressions (Landahl, 1938, p. 116):

For $\Delta < h$:

$$p = 1 - e^{-kh} \cosh k\Delta , \tag{3}$$

$$q = e^{-kh} \cosh k\Delta . \tag{4}$$

For $\Delta = h$:

$$p = \tfrac{1}{2}(1 - e^{-2kh}), \qquad q = \tfrac{1}{2}(1 + e^{-2kh}). \tag{5}$$

For $\Delta > h$:

$$p = e^{-k\Delta} \sinh kh , \tag{6}$$

$$q = 1 - e^{-k\Delta} \sinh kh . \tag{7}$$

Equations (3) and (4) as well as equations (6) and (7) reduce to equations (5) for $\Delta = h$.

The use of expression (2), while having the advantage of giving simple closed final expressions, has the disadvantage of requiring the discrimination between the three cases $\Delta < h$, $\Delta = h$, and $\Delta > h$. A convenient substitute for expression (2), which approximates a normal distribution rather well, especially for small values of ξ, is*

$$p(\xi) = A\left(\xi^4 - \alpha\,\xi^2 + \frac{\alpha^2}{2}\right), \tag{8}$$

used for values of ξ in the interval $-\sqrt{\alpha/2}$, $+\sqrt{\alpha/2}$, A and α being constants. It is readily seen that within the above mentioned interval

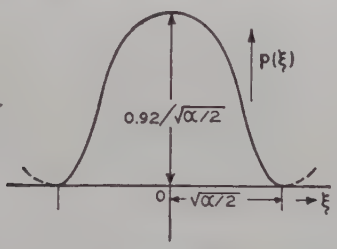

FIGURE 2

the curve $p(\xi)$ has the shape as shown on Figure 2. The use of expression (8) amounts to neglecting the very small probabilities, given by a normal distribution function, for large values of ξ. Instead of the requirement

$$\int_{-\infty}^{+\infty} p(\xi)\,d\xi = 1\,, \tag{9}$$

we now shall require

$$A\int_{-\sqrt{\alpha/2}}^{+\sqrt{\alpha/2}} \left(\xi^4 - \alpha\,\xi^2 + \frac{\alpha^2}{2}\right) d\xi = 1. \tag{10}$$

Requirement (10) leads to

$$A = 1.84\,\alpha^{-5/2}, \tag{11}$$

so that finally we have

$$p(\xi) = 1.84\,\alpha^{-5/2}\left(\xi^4 - \alpha\,\xi^2 + \frac{\alpha^2}{2}\right). \tag{12}$$

The probability p of similarity reaction is given by (Landahl, 1938; Rashevsky, 1940)

* Suggested by L. L. Thurstone. Personal communication to the author.

$$p = \int_{-(\Delta+h)}^{-(\Delta-h)} p(\xi)\, d\xi\,. \tag{13}$$

If expression (12) is used, we must always have

$$\Delta + h < \sqrt{\alpha/2}\,, \qquad \Delta \leqslant h \text{ or } \Delta = h\,. \tag{14}$$

With this restriction, we find, by introducing expression (12) into equation (13) and integrating,

$$p = 1.84\,\alpha^{-5/2}\left[2\,\Delta^4 - 2(\alpha - 2h^2)\,\Delta^2 + \left(\frac{2}{5}h^4 - \frac{2\alpha}{3}h^2 + \alpha^2\right)\right]h. \tag{15}$$

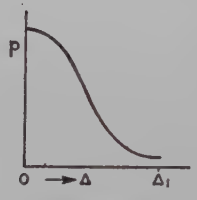

FIGURE 3

Since, because of inequality (14), $\alpha - 2h^2 > 0$, therefore p varies as a function of Δ as shown on Figure 3. By solving the equation

$$\frac{\partial p}{\partial \Delta} = 0, \tag{16}$$

we find that the curve has a horizontal tangent for

$$\Delta_1 = \sqrt{\frac{\alpha - 2h^2}{2}} < \sqrt{\frac{\alpha}{2}}. \tag{17}$$

Equation (15) has a meaning only in the interval $(0\,,\ \Delta_1)$ since for $\Delta > \Delta_1$, p, as given by equation (15), increases while it actually should drop monotonically to zero. For $\Delta = \Delta_1$, p is positive, but very small.

For later purposes we shall now derive an expression for h in terms of the thresholds of the different fibers involved.

If, with H. D. Landahl (1938), we assume that the excitatory and inhibitory fibers have the same parameters, that is, $A = B$, $a = b$, then the intensities E_{III} and $E_{IV'}$ of the fibers *III* on one hand and *III'* and *IV'* (Figure 1) on the other are given by

$$E_{III} = \beta(\varepsilon_1 - h_{III})\,; \qquad E_{IV'} = \beta(\varepsilon_2 - h_{IV'})\,. \tag{18}$$

Hence, denoting by ε_3 and j_4, the values of ε and j at the synapse s_3,

$$\varepsilon_3 = \frac{A\beta}{a}(\varepsilon_1 - h_{III}); \qquad j_4 = \frac{A\beta}{a}(\varepsilon_2 - h_{IV}'). \tag{19}$$

Therefore

$$\varepsilon_3 - j_4 = \frac{A\beta}{a}(\varepsilon_1 - \varepsilon_2) + \frac{A\beta}{a}(h_{IV}' - h_{III}), \tag{20}$$

and similarly, at the synapse s_4

$$\varepsilon_4 - j_3 = -\frac{A\beta}{a}(\varepsilon_1 - \varepsilon_2) + \frac{A\beta}{a}(h_{IV}' - h_{III}). \tag{21}$$

We do not have in general

$$\varepsilon_3 - j_4 = -(\varepsilon_4 - j_3),$$

as in Landahl's case, unless $h_{IV}' = h_{III}$, that is, unless the thresholds of the excitatory and inhibitory fibers are the same. In the general case it may happen that both $\varepsilon_3 - j_4$ and $\varepsilon_4 - j_3$ are positive and greater than h_V. This would complicate matters considerably. However, if

$$0 < \frac{A\beta}{a}(h_{IV}' - h_{III}) \leqq h_V, \tag{22}$$

then, with $\varepsilon_1 - \varepsilon_2 > 0$, we always will have

$$\varepsilon_3 - j_4 > 0, \qquad \varepsilon_4 - j_3 < h_V. \tag{23}$$

Assuming, therefore, inequality (22) to hold, we now have for the condition of a response R_Δ,

$$\varepsilon_3 - j_4 > h_V,$$

which, together with expression (20), gives

$$\varepsilon_1 - \varepsilon_2 > \frac{a}{A\beta} h_V + h_{III} - h'_{IV}. \tag{24}$$

Hence

$$h = \frac{a}{A\beta} h_V + h_{III} - h_{IV}'. \tag{25}$$

The greater the threshold of the cross-inhibitory fibers, the smaller h. The quantity h also increases with the threshold h_V.

Now we proceed with computing the probability of a similarity or dissimilarity judgment for two multimodal stimulus patterns. We may consider two different cases.

Case A. For each modality there is a separate neuron chain for a reaction R_s. The whole mechanism consists of a number of such mechanisms, as represented on Figure 1. Let the subscript i refer to the i-th modality. Then if all R_{Δ_i}'s are zero, all R_{si} are produced. If only some R_{Δ_i}'s are zero, then only some of the R_{si} are produced. With this mechanism an R_s reaction is produced whenever at least one R_{Δ_i} is zero. In other words, an individual will always notice a similarity whenever there is one in any respect.

The probability of a given Δ_i to give no difference response is $p(\Delta_i)$. The probability of a given Δ_i to give no difference response, but for all other Δ_i's to give one, is

$$p(\Delta_i) \prod_k q(\Delta_k); \qquad (k \gtrless i). \tag{26}$$

Hence the probability that any one Δ_i will give no difference response while all others will is

$$\sum_{i=1}^{i=n} p(\Delta_i) \prod_k q(\Delta_k); \qquad (k \gtrless i). \tag{27}$$

The probability that a given pair Δ_i and Δ_l will simultaneously give no probability response, regardless of what the remaining Δ_k's do, is

$$p(\Delta_i)p(\Delta_l). \tag{28}$$

The probability that the above mentioned pair gives a no difference response while all other Δ_k's do give a difference response is

$$p(\Delta_i)p(\Delta_l) \prod_k q(\Delta_k); \qquad (k \gtrless i; k \gtrless l). \tag{29}$$

Hence the probability that any one pair gives a no difference response, while all other Δ_k's give a difference response, is

$$\sum_i \sum_l p(\Delta_i)p(\Delta_l) \prod_k q(\Delta_k); \quad (k \gtrless i; k \gtrless l; i \gtrless l). \tag{30}$$

Similar expressions are obtained for the probability of any three Δ's giving a no difference response, all others giving a difference response, etc. Summing all those probabilities, we finally obtain for the total probability of a similarity response

$$P = \sum_i p(\Delta_i) \prod_k q(\Delta_k) + \sum_i \sum_l p(\Delta_i)p(\Delta_l) \prod_k q(\Delta_k) + \cdots \sum_i \cdots \sum_r p(\Delta_i) \cdots p(\Delta_r) \prod_k q(\Delta_k). \tag{31}$$

Case B. There is one common response path for R_s for all modalities (Figure 4). Now R_s is produced only when all R_{Δ_i}'s are

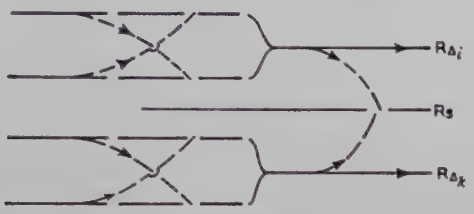

FIGURE 4

zero. Hence the total probability P of R_s is equal to the probability of all Δ_i's giving simultaneously no reaction R_Δ. This is equal to

$$P = \prod_{i=1}^{i=n} p(\Delta_i). \tag{32}$$

Using expressions (3), (5), and (6), or expression (15), for $p(\Delta_i)$, we can compute P as a function of all Δ_i's.

In order to compare equations (31) and (32) with experimental data, it is necessary to have a series of stimulus patterns with known values of Δ_i's for each pair. For some modalities the differences Δ_i's may be measured directly by the difference of some physical quantities. Thus we may have a set of objects of different size, weight, temperature, and perhaps saturation value of a given color, or still better, intensity of illumination. In some cases, however, the modalities may not be of a simple physical nature. Thus we may compare two objects in regard to the degree of their difference in being used to perform a certain function. For instance, a bell and a horn would be generally considered as more similar in regard to their use as sounding devices than a bell and a dishpan, although the latter may be used for sound-producing purposes. In such cases a scale of Δ_i values may be established by standard psychophysical methods, for instance, the rank order method or the method of paired comparisons. We may, for example, ask a large number of subjects to arrange a number of objects first in order of their use for a certain function, then in order of values of some other modality, etc. From such rankings scale values for different modalities may be computed. Then pairs of those objects may be presented to *one* test subject many times, with the request to pass a judgment of similarity or dissimilarity *in general*, and from the observed probabilities of different responses equations (31) or (32) may be compared with experiment.

Consider a stimulus pattern which becomes conditioned to a definite motor reaction, in particular to a verbal reaction. The verbal reaction is then the "name" of the stimulus pattern, and stands as a

symbol for the latter.

In general, stimulus patterns, denoted by the same word or having the same name, are somewhat different with respect to some of the component single stimuli, but they all have *some* component stimuli in common. Thus a "ball" may be large, small, white, black, made of leather or of steel, but it always has a characteristic shape.

Some attributes of an object, denoted by a given name, occur always in 100% of the cases. Some others occur less frequently. Considering each of those attributes as a component stimulus of the pattern, we may say that those component stimuli occur with different frequencies. We may arrange them in order of the decreasing frequency of occurrence and represent them as equi-distant points on a straight line, which we choose as abscissa. If we plot as ordinate the corresponding probability of occurrence, we shall obtain a line representing a monotonically decreasing function. The variable along the abscissa may be measured in terms of the arbitrary chosen distance between the points. Denote the abscissa of each point by x_i. If a is the distance between any two points, then

$$x_i = ai . \tag{33}$$

Since each x_i represents a component stimulus of the pattern, we may speak of "the stimulus x_i".

The conditioning of the stimulus pattern $S(x_1, x_2, \cdots x_n)$ to a given verbal reaction R takes place gradually, as the pattern $S(x_1, x_2, \cdots x_n)$ is experienced a sufficient number of times. Each of the component stimuli x_i of the pattern S is thus conditioned to R. It is natural to assume that the intensity $R(x_i)$ of the reaction R to the stimulus x_i will be the weaker, the smaller the frequency of occurrence of x_i in the total stimulus pattern $S(x_1, x_2, \cdots x_n)$.

Let us now consider a mechanism, discussed previously (Rashevsky, 1936, 1938; Householder and Amelotti, 1937). Let all efferent conditioned fibers send inhibitory fibers to the afferent centers of each stimulus x_i. Then a weaker stimulus x_k may be completely inhibited by the strong reactions $R(x_i)$. Let $N(x_i)$ represent the frequency of occurrence of x_i. Then the average intensity $I(x_i)$ of the stimulus x_i is proportional to $N(x_i)$ and equal to $b_1 N(x_i)$. The intensity $R(x_i)$ of the reaction R in the absence of inhibiting fibers is proportional to $I(x_i)$ and is equal to

$$R(x_i) = bI(x_i). \tag{34}$$

But since each x_i center receives inhibitory fibers from all conditioned pathways $x_i - R$, therefore, the actual excitation $I(x_i)$ is given by

$$I(x_i) = b_1 N(x_i) - \lambda \sum_i R(x_i) , \tag{35}$$

λ being a constant.

When the number of component stimuli is very large, we can replace the sum by an integral, and thus obtain

$$I(x) = b_1 N(x) - \int_0^\kappa R(x)\,dx\,. \tag{36}$$

Introducing expression (34) into (36) we obtain

$$I(x) = b_1 N(x) - \lambda b \int_0^\kappa I(x)\,dx\,. \tag{37}$$

The upper limit is determined by considerations that those x's, which are completely inhibited, do not produce any $R(x)$ and do not therefore contribute anything to the inhibition of others (Rashevsky, 1938, chap. xxviii).

As an illustration we shall discuss here the case when

$$N(x) = e^{-\beta x}\,. \tag{38}$$

A component stimulus corresponding to $x = 0$ occurs then every time, the probability of its occurrence being *1*. This assumption simplifies the following equations considerably, but does not introduce any limitation in principle. We then have (Rashevsky, 1938, pp. 282-283)

$$I(x) = b_1 (e^{-\beta x} - e^{-\beta \kappa}), \tag{39}$$

where κ is the root of the equation

$$e^{\beta\kappa} - \beta\kappa - 1 = \frac{\beta}{b\lambda}. \tag{40}$$

It is readily seen (Rashevsky, 1938, p. 283) that κ decreases with increasing λ.

We can find two approximate solutions of equation (40), one for the case that β is very large, $\beta/b\lambda > 0$; and another for very small values of β.

In the first case we may neglect in equation (40) $\beta\kappa$ and 1 compared with $e^{-\beta\kappa}$. We then have

$$e^{\beta\kappa} = \frac{\beta}{b\lambda}, \tag{41}$$

or

$$\kappa = \frac{1}{\beta} \log \frac{\beta}{b\lambda} > 0. \tag{42}$$

In the second case we expand $e^{\beta\kappa}$, omitting terms of third and higher powers. This gives

$$\kappa = \sqrt{\frac{2}{b\beta\lambda}} . \tag{43}$$

In any case, for very large values of λ, that is, for very strong inhibition, κ will be very small, and only those component stimuli will remain uninhibited which have a very small x, that is, which occurs either always or almost always.

With the above mechanism only such components of S will be associated with the reaction R, which occur either always or almost always. Such components may be termed "essential", the remaining ones, "accidental". We have here a rudimentary mechanism of abstraction. The verbal reaction R is now associated not with the whole accidental complex of component stimuli, entering into S, but only with the essential ones. Thus a mathematical biophysicist considers as the only essential feature of the cell its metabolism, this being the only feature which invariably occurs in all cells (Rashevsky, 1938, 1940). An individual with a large λ and hence a small κ will abstract only such features which occur always. Individuals with smaller λ may, at least off hand, include amongst "essential" features of an object, which occur very frequently, but not always. Individuals with very small λ and large κ, will show inability to abstract, and will consider as essential components even such which occur rather unfrequently.

If λ is constant, then κ is constant, too. Any component whose frequency of occurrence $y(<1)$ is greater than $e^{-\beta\kappa}$ would be considered as essential, all others, as accidental. But λ, which is a measure of the inhibitory effect, may fluctuate itself due to statistical physicochemical fluctuations in the organism. Then κ will fluctuate also. Under those conditions a component stimulus with a frequency y of occurrence may sometimes be considered as essential, sometimes as not. We may now compute the probability P_e for a stimulus of a given y to be considered essential, or the probability $P_u = 1 - P_e$ of it being considered unessential.

Let the probability of λ having a value between λ and $\lambda + d\lambda$ be $p(\lambda)\,d\lambda$, with $p(0) = p(\infty) = 0$, and consider the most likely case that $p(\lambda)$ has one and only one maximum at $\lambda = \lambda_0$. The probability $p_1(\kappa)\,d\kappa$ of κ having a value between κ and $\kappa + d\kappa$ is obtained by substituting into $p(\lambda)\,d\lambda$ the expression of λ and $d\lambda$ in terms of κ and $d\kappa$, obtained from either equation (42) or (43). We shall use here as an illustration equation (43). It gives

$$\lambda = \frac{2}{b\,\beta\,\kappa^2}; \qquad d\lambda = -\frac{4\,d\,\kappa}{b\,\beta\,\kappa^3}. \tag{44}$$

Hence

$$p_1(\kappa)\,d\kappa = -\frac{4}{b\,\beta}\,p\left(\frac{2}{b\,\beta\,\kappa^2}\right)\frac{d\,\kappa}{\kappa^3}. \tag{45}$$

The abscissa x of a component of frequency y is

$$x_y = -\frac{1}{\beta}\log y > 0. \tag{46}$$

The component is considered as essential everytime when $\kappa > x_y$. Hence the probability P_e is given by

$$P_e = \int_{-x_y}^{\infty} p_1(\kappa)\,d\kappa = -\frac{4}{b\,\beta}\int_{-(1/\beta)\log y}^{\infty} p\left(\frac{2}{b\,\beta\,\kappa^2}\right)\frac{d\,\kappa}{\kappa^3}. \tag{47}$$

Expression (47) gives us P_e in terms of β, which characterizes the external stimulus S, and in terms of the parameters of $p(\lambda)$, which contain the individual constants, in particular, λ_0. If $p(\lambda)$ is some kind of an exponential, P_e could not be evaluated in a closed form. If, however, the fluctuations of λ are approximately symmetric with respect to λ_0, then we may put $\lambda = \lambda_0 + \lambda'$ and consider that the probability of a given λ' is represented by equation (12), in which we put $\xi = \lambda'$. We now have, by substituting in equation (43), $\lambda' + \lambda_0$ for λ:

$$\lambda' = \frac{2}{b\,\beta\,\kappa^2} - \lambda_0; \qquad d\lambda' = -\frac{4\,d\,\kappa}{b\,\beta\,\kappa^3}. \tag{48}$$

Due to the approximation introduced in equation (12), we now have $P_e = 1$ for $x_y < \lambda_0 - \sqrt{\alpha/2}$ and $P_e = 0$ for $x_y > \lambda_0 + \sqrt{\alpha/2}$. For $\lambda_0 - \sqrt{\alpha/2} < x_y < \lambda_0 + \sqrt{\alpha/2}$ we have

$$P_e = -\frac{4}{b\,\beta}\int_{-(1/\beta)\log y}^{\lambda_0\sqrt{\alpha/2}} p\left(\frac{2}{b\,\beta\,\kappa^2} - \lambda_0\right)\frac{d\,\kappa}{\kappa^3}. \tag{49}$$

With $p(\lambda')$ given by equation (12), P_e can be expressed in closed form.

Equation (47) or (49) can be compared with experiments. The quantity β can be controlled in principle. Thus we may show to a subject a large number of times the same object with different accidental characteristics. In a selected number of cases, for instance, the object will be green; in another selected number of cases it will be red; in some cases it will be made of wood; in some of metal, etc. We thus can artificially "construct" the function $e^{-\beta x}$, or for that matter, any function $N(x)$. Expressions for P_u and P_e may be derived in prin-

ciple for any $N(x)$. After having presented the object a large number of times, we may ask the individual whether a given property, say, green, is an essential characteristic of the object or not. By recording the frequency of different replies, we may compare equations (47) or (49) or any other corresponding equation with experiment. We thus have a method of measuring quantitatively the ability to abstract. From such measurements some individual parameters of the subject may be calculated.

In the following we shall consider the case of such a large λ that only those component stimuli which occur always in S remain excited.

Let us denote by S' a stimulus pattern which consists of any stimuli lying in the interval $(0,\kappa)$. Denote by S'' any stimulus pattern composed of stimuli lying outside of the interval $(0,\kappa)$. We see that while S' is *always* contained in S, S'' is only *sometimes* contained in S. In other words, we may say that "all S's imply S'", but only "some S's imply S''".

Suppose that each peripheral afferent neuron sends off two branches, one to a goup A of neurons, another to a group S. Let A and S be identical in structure except for one thing. While each neuron of A receives from each corresponding efferent an inhibitory fiber, such as discussed above, the neurons of S do not receive such inhibitory fibers. Let, however, each neuron of group A send to its corresponding neuron of group S a *strongly* inhibiting fiber. According to what we have said above, when a stimulus pattern S is presented, the individual neurons in A which correspond to any stimulus S'' will be completely inhibited, while those corresponding to stimuli S' will be excited. In S, therefore, all neurons corresponding to S' will be inhibited, while those corresponding to S'' will be excited. Let nerve pathways lead from both A and S to different conditioning centers; and let each pair of pathways leading from A and S to any given conditioning center cross-inhibit each other so that only one of them can be conducting, the one which is more strongly excited. Let the neurobiophysical process corresponding to our experiencing of the concept "all S's" consist in a stronger excitation of the pathway leading from A to any conditioning center; while the process corresponding to our experiencing of the concept "some S's" consists in a stronger excitation of the pathways leading from S.

If now any of the stimulus patterns S' or any of their parts are associated through the proper conditioning center to any other stimulus pattern S_1, then the neurobiophysical process corresponding to the concept "all S's" will evoke also the stimulus S_1. If any of the patterns S'' or any of their parts are associated with any other stimu-

lus S_2, then the neurobiophysical process corresponding to "some S's" will evoke S_2. We thus have a neurobiophysical mechanism corresponding to the notions, "all S's imply S_1" and "some S's imply S_2".

If a stimulus pattern S as such is presented, without specifications such as "all" or "some", then, according to the above, the A and S centers will be equally excited, and due to mutual inhibition, none of the pathways from either A or S will transmit. This would mean simply that "S" cannot imply anything. This is not as paradoxical as it sounds. When we say "S implies S_1" we really mean "all S's imply S_1", the conventional rules of the language permitting the omission of "all". In other words, due to proper conditioning, omission of any specification results in an increased stimulation of A.

The stimulus S_1, produced indirectly, or "by implication", itself will excite corresponding groups A_1 and S_1; through any of those a stimulus S_3 may be "implied", etc.

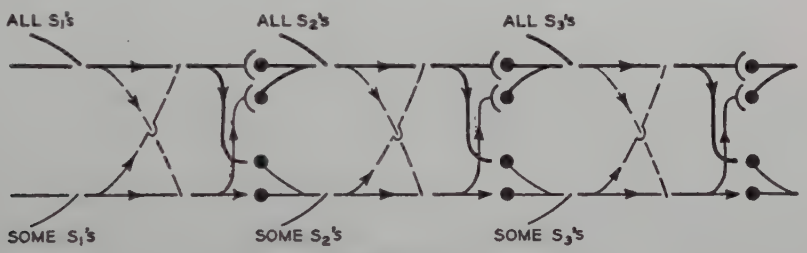

FIGURE 5

Now consider such a chain of double pathways in which every preceding stimuli implies every following, as shown in Figure 5. The A and S pathways are symbolized by single fibers. Let each A fiber excite strongly every other A fiber, with which it synapses. But let an S fiber be only weakly excited, or not excited at all, by either an A or an S fiber. This can be achieved by making all S fibers have rather high thresholds, or by having two synapses excite every A fiber, but only *one*, every S fiber (Figure 5). In that case we have the following scheme:

All	S_1's	imply	S_2;	all	S_2's	imply	S_3;	all	S_1's	imply	S_3.
Some	S_1's	"	S_2;	"	"	"	"	some	"	"	"
All	"	"	"	some	"	"	"	no implication			.
Some	"	"	"	"	"	"	"	"	"		.

The above scheme represents correctly some simple modes of logical reasoning.

We may consider a chain consisting of any number n of such "elements" or "links" as represented on Figure 5. A functioning of

such a chain will correspond to a reasoning by a simple successive chain of syllogisms.

In the further development of the theory it will be necessary to suggest a mechanism for "No S implies S_1" and for "Some S's do not imply S_1". Instead of two parallel chains of cross-inhibitory fibers, we shall have four chains. The treatment may have to follow the way indicated for the theory of discrimination between several stimuli by H. D. Landahl (1938). The problem may also offer a test for the heuristic value of the method of W. S. McCulloch and W. Pitts (1943). Those authors show that by applying logical calculus, it is possible to construct any complicated network having given properties. One could attempt to construct by the method of McCulloch and Pitts a network that would represent all modes of logical reasoning, and then apply the usual methods of mathematical biophysics to derive some quantitative relations between different manifestations of the processes of logical thinking (Landahl, McCulloch, and Pitts, 1943).

Leaving all such developments for the future, we shall derive here some quantitative relations for the simple and incomplete scheme suggested above. Those relations are perhaps to be considered now as illustrations only.

Each of the links of the chain, represented in Figure 5, is essentially a circuit similar to the one represented on Figure 1 and has accordingly a characteristic threshold h. We shall now consider the case when all h's are the same. The differences in the intensities of excitation of the A's and S's correspond to the difference $\Delta = \varepsilon_1 - \varepsilon_2$ in Figure 1. We shall assume that $\varepsilon_1 - \varepsilon_2$ is a constant quantity, the same for all links. This will happen if the afferent ends of the fibers in each link will reach their saturation values E_a for rather small values of the stimulus (Rashevsky, 1938, chap. xxii). The synapses at which ε_1 and ε_2 are considered shall be referred to as synapses s_1 and s_2 correspondingly. The intensities of excitation of the fibers going from those synapses will be denoted by E_1 and E_2.

Let each link send inhibitory fibers to all others, those inhibitory fibers rising the thresholds h. If n is the number of active links in the chain, the threshold of each will be given by

$$h = h_0 + a(n-1), \tag{50}$$

where h_0 and a are constants.

We may also consider the following interactions of the different links.

Let the relation between $\varepsilon - h$ and E at the synapses s_1 and s_2 be not linear, but represented by a curve which is convex upward

(Rashevsky, 1938, chap. xxii). Then an equal increase in ε_1 and ε_2 will have the same effect upon $E_1 - E_2$ as if $\varepsilon_1 - \varepsilon_2$ were decreased. If each link is connected with each other by excitatory fibers acting on the synapses s_1 and s_2, then the larger n, the larger ε_1 and ε_2, and the smaller the difference $E_1 - E_2$. But it is that latter quantity rather than $\varepsilon_1 - \varepsilon_2$ that determines Δ. Only when $\varepsilon \propto E$ can Δ be substituted for $E_1 - E_2$. Hence now the larger n, the smaller the "effective" Δ. Within a limited range things happen formally as if Δ decreases with n, and we may put approximately

$$\Delta = \Delta_0 - b(n-1). \tag{51}$$

We have the following expressions for the probabilities p_c, p_d, and p_w of a correct, doubtful, or wrong response for each separate link of the chain (Landahl, 1938):

For $\Delta > h$	For $\Delta < h$	
$p_c = 1 - \frac{1}{2}e^{-k(\Delta-h)}$;	$p_c = \frac{1}{2}e^{-k(h-\Delta)}$;	(52)
$p_d = e^{-k\Delta}\sinh kh$;	$p_d = 1 - e^{-kh}\cosh k\Delta$;	(53)
$p_w = \frac{1}{2}e^{-k(\Delta+h)}$;	$p_w = \frac{1}{2}e^{-k(\Delta+h)}$.	(54)

We now may compute the probabilities P_c, P_d, and P_w of a correct, doubtful, or wrong response for the whole chain of n elements.

Barring for the present the relatively unlikely case that several wrong conclusions combined give a correct one, we find that a correct total response requires a simultaneous correct response in all links. Hence

$$P_c = p_c^n. \tag{55}$$

A wrong response in the whole chain is obtained when either one link gives a wrong response, all the others giving a correct one, or any two links give a wrong response, all others a correct one, etc. But if a single link in a chain does not respond at all, the whole chain will give no response. Hence, by using an argument similar to that which led us to equation (31) and remembering that the constants of all links are now assumed to be equal, we find

$$P_w = np_w p_c^{n-1} + \frac{n(n-1)}{2} p_w^2 p_c^{n-2} + \frac{n(n-1)(n-2)}{3} p_w^2 p_c^{n-3} + \cdots. \tag{56}$$

Similarly, an expression for P_d may be derived. We always have $P_c + P_w + P_d = 1$.

Introducing expression (50) and (51) into expressions (52), (53), and (54) and the latter into expressions (55) and (56), we thus obtain expressions for P_c, P_w, and P_d in terms of the number n of inferences in the whole chain of reasoning, as well as of the "individual" constants Δ, h, a, b, and k. Such expressions may be verified experimentally, and from the comparison of the theory with experiment, some of the individual constants may be computed.

Similar expressions may be obtained for a more general case when the process of reasoning is not necessarily constituted of a simple chain of consecutive inferences. Expressions (50), (51), and (52) —(54) still hold for each individual inference. In general expression (55) for P_c also still holds, but the probabilities P_w and P_d must be now computed in a different way depending on the "structure" of the logical problem. Now, for instance, some inferences of the pattern may give no response, yet the pattern as a whole still results in a total inference. For each type of logical problem we may, however, compute the values of P_c, P_w, and P_d, and again we may compare our theoretical results with experimental data.

It must be emphasized that the derivations of equation (55) and (56), or any other similar expressions, is entirely independent of the assumed mechanism of the individual link, which provides for a simple inference. The same method for deriving the probability of correct, wrong, or no response in a chain of syllogism may be applied to any other mechanism, which is assumed for the elementary act.

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THE DIFFERENTIAL DIFFERENCE EQUATION FOR EPIDEMICS

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In a series of recently published papers E. B. Wilson and his collaborators have investigated some of the mathematical questions connected with epidemics. A differential difference equation was set up and various properties of its solution were obtained. This equation implies that the epidemic has an equilibrium state, and it is the purpose of this note to show that this equilibrium is stable in the sense that any small deviation from it will tend to zero.

If we let $S(t)$ denote the number of susceptible persons present at time t, A denote the rate of recruitment of new susceptibles, τ denote the time after infection when an infected person becomes infectious, σ denote the duration of the disease, and r denote the number of susceptibles being infected per infectious person per susceptible person per unit of time, then it has been shown (Wilson and Worcester, 1944) under the assumption that A, τ, σ, and r are constant that

$$A - dS/dt = rS(t)\,[A\,\sigma - S(t-\tau) + S(t-\tau-\sigma)]. \qquad (1)$$

The equilibrium value of S is clearly $S = 1/r\sigma$ if $Ar\sigma > 0$. We shall explicitly make this assumption. The method of determining whether or not this equilibrium is stable is standard (see, for example, Goursat, 1927). We write the equation of variation of the equation (1), namely

$$dx/dt = -Ar\sigma x + \sigma^{-1}[x(t-\tau) - x(t-\tau-\sigma)], \qquad (2)$$

and seek to find solutions of this equation of the form $x(t) = e^{at}$. Such a function will be a solution of equation (2), if, and only if, a is a solution of the secular equation

$$e^{-a\tau} - e^{-a(\tau+\sigma)} = (a + Ar\sigma)\,\sigma. \qquad (3)$$

The equilibrium will be stable in case every solution a of equation (3) has a negative real part. This fact we shall now prove.

Suppose first that a is a nonnegative real number. Then it follows from the inequalities,

$$e^{-a\tau}(1-e^{-a\sigma}) \leqq 1-e^{-a\sigma} \leqq a\sigma < (a+Ar\sigma)\sigma\,,$$

that a can not satisfy equation (3). Similarly, if a is a negative real number, then we have

$$-e^{-a\tau}(e^{-a\sigma}-1) < -(e^{-a\sigma}-1) < a\sigma < (a+Ar\sigma)\sigma.$$

It follows that equation (3) has no real roots at all. To find the complex roots, let $a = b + ic$, where b and c are real. Then equation (3) is equivalent to

$$e^{-b\tau}\cos c\tau - e^{-b(\tau+\sigma)}\cos c(\tau+\sigma) = (b+Ar\sigma)\sigma, \tag{4}$$

$$e^{-b(\tau+\sigma)}\sin c(\tau+\sigma) - e^{-b\tau}\sin c\tau = c\sigma\,. \tag{5}$$

Since there are no real roots, we have that $c \neq 0$, and we may assume without loss of generality that $c > 0$. Equation (5) may be written in the following form:

$$\int_{\tau}^{\tau+\sigma} g(x)\,dx = \int_{\tau}^{\tau+\sigma} e^{-bx}(c\cos cx - b\sin cx)\,dx = c\sigma\,. \tag{6}$$

We shall show that $g(x) \leqq c$ when $b \geqq 0$, with the strict inequality holding at all except a finite number of points on the interval $(\tau, \tau+\sigma)$. This will show that equation (6), and consequently equation (5), can not be true when $b \geqq 0$.

Now $g'(x) = e^{-bx}[(b^2-c^2)\sin cx - 2bc\cos cx]$ vanishes if, and only if, $\sin cx = \pm 2bc/(b^2+c^2)$, $\cos cx = \pm (b^2-c^2)/(b^2+c^2)$, and then $g(x) = \pm c\,e^{-bx} \leqq c$. It follows that the relative maxima of the function $g(x)$ are all less than or equal to c. Therefore, $g(x)$ is itself less than c except for at most a finite number of points on the interval $(\tau, \tau+\sigma)$.

We have now shown that any solution (b,c) of equations (4) and (5) is such that $b < 0$. Since b is the real part of a, the equilibrium solution of equation (1) is stable. Moreover, since $c \neq 0$, a small perturbation from the equilibrium will have roughly the form of an exponentially damped oscillation.

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A REINTERPRETATION OF THE MATHEMATICAL BIOPHYSICS OF THE CENTRAL NERVOUS SYSTEM IN THE LIGHT OF NEUROPHYSIOLOGICAL FINDINGS

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The fundamental equations for the interaction between neurons used in mathematical biophysics seem at first incompatible with the actual neurophysiological findings on the synaptic transmission. It is shown, however, that those equations may be readily interpreted in terms of accepted neurophysiological views. What has been termed "synapse" in mathematical biophysics must be regarded as a complicated network of internuncial neurons. It is shown that, under rather general conditions, the number of those interneurons will *statistically* vary with time according to the differential equation postulated for the excitatory and inhibitory factors. The latter are thus interpreted as the number of excitatory and inhibitory interneurons.

When the fundamental postulates of the mathematical biophysics of the central nervous system were first developed *in abstracto* (Rashevsky, 1938), they were suggested, on the one hand, by the earlier observations of E. D. Adrian (1932) regarding the relation between frequency of discharge in a peripheral fiber and the intensity of the stimulus; on the other hand, by a possible generalization of the two-factor theory of peripheral excitation. The earlier abstract developments of the theory were not too much concerned with the direct relation of the fundamental postulates to actual observations: the main interest centered around the proof that very complicated phenomena could be systematically described by a rather simple system of postulates. When, however, some of the consequences of the theory, elaborated principally by A. S. Householder and H. D. Landahl, turned out to be in good agreement with actual observations (Rashevsky, 1940), it became evident that the postulated equations are something more than mere mathematical assumptions. Yet those postulates seemingly did not agree with the accumulated experimental evidence on the interaction of two neurons at the synapse, as well as with other observations. It was pointed out, therefore (Rashevsky, 1940, p. 125 ff.), that the postulated two factors, the excitatory ε and the inhibitory j, may actually be not simple physicochemical entities, but rather complex ones, and that the fundamental equations governing their variation with respect to time and their action may be considered as

convenient and useful *formal* postulates which eventually would have to be interpreted through some perhaps rather complicated mechanism. In the meantime, the development of the theory could go ahead, regardless of the actual true mechanism, just as the development of a number of formal physical theories proceeded before actual atomic interpretations were formed.

Eventually the usefulness of the postulates became firmly established (Householder and Landahl, 1945; Rashevsky and Brown, 1944a, b). At the same time W. S. McCulloch and W. Pitts (1943), using Boolean algebra, developed a theory of nervous activity which was based more directly on observations about synaptic transmission. All the successful applications of the older postulates of mathematical biophysics of the central nervous system remained outside of the scope of this new theory, although some suggestions as to how the apparent gap between the two approaches may be bridged were made by H. D. Landahl, W. S. McCulloch, and W. Pitts (1943; c.f. also Householder and Landahl, 1945). It is the purpose of this paper to show how the two approaches can be connected, and how the fundamental postulates used hitherto can be reconciled with neurophysiological findings.

The relation between frequency of discharge and intensity of a continuous stimulus postulated in mathematical biophysics holds only in a limited sense, and in a limited number of cases. For slowly adapting fibers, such as those of the muscle end organs (Fulton, 1943; Mathews, 1931a, b; 1933), the postulated relations hold for a constant stimulus except for the short period of the initial volleys of higher frequency. They also may hold in some cases of visual stimuli (Hartline and Graham, 1932). For the fibers of the acoustic nerve, the relation between the intensity of the stimulus and frequency of response is very similar to that postulated in mathematical biophysics, but the thing is complicated by the fact that the frequency of the sound enters as a parameter (Galambos and Davis, 1943). On the other hand, for rapidly adapting fibers such as those conveying the sensation of touch (Cattell and Hoagland, 1931), the postulated relations do not hold even with remote approximation.

Thus while for slowly adapting fibers the postulated relation between frequency of discharge and intensity of stimulation (Rashevsky, 1938),

$$\nu = \alpha h \log \frac{S}{h} \quad \text{or} \quad \nu = \frac{1}{\theta}\left[1 - e^{-\alpha\theta(S-h)}\right], \tag{1}$$

may hold fairly well for constant S, they certainly do not hold for sufficiently rapidly varying values of S. Formally, however, this may

be remedied by considering the rate of change $\dot{S} = dS/dt$ itself as a stimulus and considering a fiber as reacting both to the stimulus S and dS/dt. Very rapidly adapting fibers like those of the tactile receptors, which do not discharge at all for continuous stimuli (Cattell and Hoagland, 1931), may be considered as responding to $\dot{S}$ only. It can be shown that these formal assumptions are made plausible biophysically by considerations of the two-factor theory of peripheral nerve excitation. Such considerations also throw light on the facts mentioned in the preceding paragraph.

An actual stimulus usually involves a very large number of fibers, this number increasing with the intensity due to the distribution of thresholds. Therefore, even if we have a number of perfectly adapted fibers, each of which responds to a continuous stimulus with a frequency independent of the intensity S, still the total number ν_T of impulses per unit time for the whole set of fibers will increase with S, the relation between ν_T and S being given for physiological reasons by a curve convex upward, except perhaps in the neighborhood of the threshold. Hence, if the actual units which correspond to the "fiber" of the mathematical biophysicist are not fibers but *large groups of fibers*, then for such groups the relations (1) will still hold with sufficient approximation, h denoting now the lowest threshold of the group.

The problem of synaptic transmission is more complicated. The synaptic delay between two actual neurons is of the order of 0.5 ms, and practically independent of the intensity of the stimulus (Lorente de Nó, 1935a, b, c, 1938a, b, c). The frequency of a presynaptic discharge is not modified at the synapse, at least in sympathetic ganglia (Bronk, 1939). On the other hand, the time constants for the excitatory and inhibitory factors, calculated by H. D. Landahl (1939; also Householder and Landahl, 1945) from comparison of theory with experiment are found to be sometimes of the order of seconds. Apparently, the abstract "synapse" of the mathematical biophysicist must involve a very large number of actual neurons. In the following, for precision, wherever we use the word synapse, we shall mean the actual synapse of the neurophysiologist. The word "synapse" in quotation marks will refer to the abstract concept of the mathematical biophysicist.

Consider either a single very slowly adapting fiber, or a group of parallel fibers I (Figure 1) stimulated with an intensity S. The total average number of impulses per unit time in that fiber, or group of fibers, will then be a monotonically increasing function of S, described approximately by one of equations (1). Let each fiber of the group send off a large number of collaterals, each forming a chain of

neurons I', as indicated in Figure 1. Each chain may in general contain a different number of neurons. Let the axons of the last neurons of each of those chains end on a surface P, and let the collaterals of all the fibers I be thoroughly "mixed" in the surface P so that each element of area ΔP receives collaterals from all the fibers I. Due to slight variations in the individual synaptic delays of the different neurons, even a regular sequence of impulses in a fiber I will not result in a set of synchronous impulses arriving at the surface P. This will hold *a fortiori* for the impulses arriving at P from different fibers I

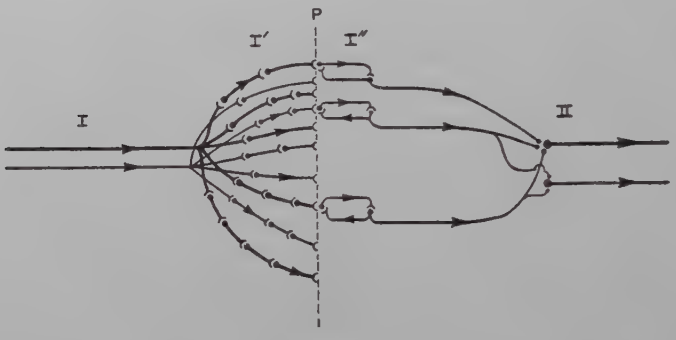

FIGURE 1
For simplicity, only two fibers of pathway I and their branches are shown in the drawing. For the same reason, only three circuits I'' are shown.

if the frequencies of discharges of the latter are statistically independent. Hence the surface P will receive a large number of impulses per unit time, this number being constant only on the average. But this average number $\bar{\nu}$ will be proportional to the total average frequency ν_T in the group of fibers I.

Let each axon of the system I' form in the surface P a synapse with a neuron I'', which forms a closed chain of two or more neurons.

Let each axon of I' excite the corresponding neuron I'' just above the threshold so that relatively slight accidental fluctuations of the thresholds of I'' may make them occasionally unexcitable by I'. Let α denote the probability that an impulse arriving at P excites the corresponding I''.

Consider the case in which all the neurons I'' are unexcited before the application of the stimulus S. After S is applied, a circuit connected to I'', is thrown into a permanently excited state every time an impulse arriving at P excites a neuron I''. If N_0 denotes the total number of neurons I'' available at P, and N_i denotes the number al-

ready excited, then the number of circuits thrown into an excited state during the time dt is $dN_i = \alpha\, \bar{\nu}(N_0 - N_i)\, dt$. If, for reasons which will be explained presently, N_i always remains much less than N_0, in other words, when the total reserve of available neurons N_0 is very large, then we have approximately

$$\frac{dN_i}{dt} = \alpha\, \bar{\nu}\, N_0. \tag{2}$$

But $\bar{\nu}$ is proportional to ν_T, and the latter is taken to be a measure of the intensity E of excitation of the whole pathway I. Hence, denoting by A a constant:

$$\frac{dN_i}{dt} = AE. \tag{3}$$

Each of the circuits, once excited, would remain so indefinitely if everything within it and its environment were constant. But such a constancy as a rule never occurs in biological systems. Thresholds fluctuate even in controlled experiments (Pecher, 1939; Landahl, 1941). It may be that the number of terminal bulbs exciting each neuron in the circuit is so much larger than the necessary minimum one (Lorente de Nó, 1939, p. 405) that every neuron receives a highly superthreshold excitation. A slight variation in the threshold in such a case will not affect the reverberation of the circuit. But if the number of the terminal bulbs is just sufficient to excite, then a slight variation in threshold, or an accidental failure of only a few terminal bulbs to function will break the circuit and bring it back into the unexcited state. It may be worth calling attention to the fact that at ordinary values of the pH there is about one hydrogen ion per terminal bulb. The number of molecules of other substances may be also very small. The physicochemical conditions of a single terminal bulb must therefore fluctuate very strongly.

We thus see that depending on the number of the terminal bulbs, the circuits will possess a greater or lesser degree of instability. Due to accidental fluctuations, there will always be a probability of a number of excited circuits to be spontaneously broken during the interval of time dt. The probability for a given circuit to fail within the interval dt is constant and equal to $a\, dt$, a being a coefficient of proportionality. Hence, the natural "rate of decay" of the excited circuits will be proportional to their total number N_i. Therefore, when due to impulses arriving from I', a certain number of circuits is thrown per unit time into the excited state, the rate of change of N_i is given by

$$\frac{dN_i}{dt} = AE - aN_i. \tag{4}$$

But this is formally identical with the differential equation for ε or j.

If the re-entrant part of each circuit sends off excitatory fibers, as shown in Figure 1, which converge upon a group of fibers *II*, then the total intensity of excitation of *II* will be at any moment a linear function of the number N_i of excited circuits. On the other hand, if the circuits send off *inhibitory* fibers to *II*, we have an inhibition proportional to N_i. In view of D. Lloyd's (1941) work, we assume with W. S. McCulloch and W. Pitts (1943) the existence of specific inhibitory fibers, rather then explain inhibition by the action of special internuncials. This assumption is, however, irrelevant for the general argument.

Equation (4) holds only approximately when $N_i << N_0$, or which is the same, when $AE/a << N_0$. For very high intensities E of excitation, equation (4) will have to be modified. The fact that equations of the form (4) can be used successfully for ε and j within a rather wide range of E indicates that N_0 is very large.

If no other limitations, except the obvious one, $N_i < N_0$, are imposed upon N_i, then we have instead of equation (4) the following:

$$\frac{dN_i}{dt} = \alpha \bar{\nu} N_0 - (\alpha \bar{\nu} + a) N_i. \tag{5}$$

Since $\bar{\nu} \propto E$, so that $\alpha \bar{\nu} = cE$, we may write the solution of equation (5) for a constant E and for $N_i(0) = 0$ as follows:

$$N_i = \frac{cN_0 E}{cE + a} [1 - e^{-(cE+a)}]. \tag{6}$$

The time constant now depends on E and hence on the intensity S of the stimulus. Equation (6) reduces to the usual form for ε (or j) when $cE << a$; $cN_0 = A$. It would be of interest to look for possible indications of an increase of the time constants for very strong stimuli. This would show, for instance, on reaction times, which should decrease more rapidly for very high values of S than predicted by the usual theory (Landahl, 1938; Householder and Landahl, 1945).

FIGURE 2

Instead of assuming that neurons I'' form parts of closed circuits [interneurons C of R. Lorente de Nó (1938c, p. 210; 1939, p. 427)], we may consider them as having a structure shown on Figure 2 [Type M of R. Lorente de Nó (1938c, p. 210; 1939, p. 427)]. Such a group, if excited at a time t, will send a regular train of impulses to a neuron of II on which it converges, for a time equal to $r\sigma$, where r is the number of branches and σ the synaptic delay. Such a group has always a finite life span equal to $r\sigma$. If, however, the probability of the spontaneous failure of any one synapse of the group is large enough, the "natural" life span may practically never be reached. If the "average" life span of such a group, determined by the probability of failure of a synapse, is much smaller than the "natural" life span, then again the rate of decay of such excited groups will be proportional to their number.

We thus are led to interpret ε and j as a measure of the number of excited groups of interneurons of a certain type. Since the stability of such groups may vary within a very wide range, we obtain a very wide range of variation for the "synaptic" delay referred to in mathematical biophysics. The "synapse" of the mathematical biophysicist includes all interneurons between I and II (Figure 1). In some cases it may include a large portion of the brain. This throws light on the puzzling situation that reaction-times are correctly described quantitatively by the mathematical biophysics of a two-neuron arc with a single "synapse", although actually a large number of synapses is involved (Rashevsky, 1940).

In the light of all the above, it is suggested that in mathematical biophysics the word "connection" be substituted for "synapse", and the word "pathway" for "fiber". The word "neuron" should be retained only in its exact anatomical sense. "Group of neurons" or "macroneuron" should be used otherwise.

In all cases, when we deal with very large numbers of afferent and efferent neurons, we may continue to use the fundamental equations of mathematical biophysics, with possible improvements that may be suggested by the present interpretation. Whenever we deal with phenomena involving relatively few neurons the method of W. S. McCulloch and W. Pitts will be used. The situation reminds us of the parallel use of thermodynamics and kinetic theory in physics, depending on the nature of the problem treated.

In particular, in discussing closed circuits, we must keep in mind the difference between the "microscopic" and macroscopic" circuits, or "circuits of individual neurons" and "circuits of pathways". A single neuron cannot form a self-exciting circuit because the excitation will fall within its own refractory phase. But a group of neu-

rons, or a "macroneuron" may well be circuited in itself (Householder and Landahl, 1939). It is likely that such circuits as were designated by *Eng* in a previous paper (Rashevsky, 1945) are to be conceived as "microcircuits", while closed circuits discussed in the same paper and assumed to connect different regions of the brain (*loc. cit.*, Figure 7) are to be considered as circuits of pathways.

One interesting consequence may be noted. If ε and j measure the number of excited groups of interneurons, then the statistical fluctuations of ε and j in the stationary state, such as introduced by H. D. Landahl (1938, also Householder and Landahl, 1945) follow immediately from the above picture. Both the building up of ε or j, as well as their decrease follow equation (2) only statistically. The decay, for instance, does not proceed *exactly* according to an exponential. If $\bar{m}$ in the average number of groups decays during the time t, that is,

$$\bar{m} = aN_i t , \tag{7}$$

then (Bothe, 1926) the probability that in the interval t *actually* m groups will decay is given by

$$p_m = \frac{\bar{m}^m}{m!} e^{-\bar{m}}, \tag{8}$$

or for large values of $\bar{m}$,

$$p_m = \frac{1}{\sqrt{2\pi\bar{m}}} e^{-\frac{(m-\bar{m})^2}{2m}} . \tag{9}$$

Denoting by Δ_m the average absolute deviation $m - \bar{m}$, we have for the relative variation,

$$\Delta_m/\bar{m} = 1/\sqrt{\bar{m}} . \tag{10}$$

Due to the fluctuation of the decay, the stationary values of ε and j will also fluctuate even if the building-up rate were constant. The fluctuation of the latter will complicate the picture further. But in general, we shall find that the fluctuations will decrease with increasing ε and j. Such relations may be in principle verified experimentally by comparing theoretical and experimental data for psychophysical discriminations, as has been done by H. D. Landahl (1938; also Householder and Landahl, 1945), but using a very wide range of intensities of stimuli.

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